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DOES NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) USE  
AFFECT DEMENTIA PROGRESSION AND SURVIVAL RATES  
IN ALZHEIMER'S DISEASE? THE CACHE COUNTY STUDY

by

Trevor Buckley

A dissertation submitted in partial fulfillment  
of the requirements for the degree

of

DOCTOR OF PHILOSOPHY

in

Psychology

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Logan, Utah

2011

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## ABSTRACT

Does Non-Steroidal Anti-Inflammatory Drug (NSAID) Use  
Affect Dementia Progression and Survival Rates in  
Alzheimer's Disease? The Cache County Study

by

Trevor Buckley, Doctor of Philosophy

Utah State University, 2011

Major Professor: Dr. JoAnn T. Tschanz  
Department: Psychology

Alzheimer's disease (AD) has multiple factors that contribute to the disease process. Among these is a state of chronic inflammation that is endured by the brain during the aging process. The use of non-steroidal anti-inflammatory drugs (NSAIDs) decreases the amount of neuroinflammation sustained by the brain, and greater levels of NSAID use have been demonstrated to be associated with decreased probability of developing AD. This study looked at whether greater rates of NSAID use were also associated with decreased rates of cognitive and functional decline and survival in a population-based sample of persons with AD. Linear mixed models failed to find any association between any NSAID use, duration of use, or timing of use (before or after AD onset) and cognitive and functional outcomes. Cox regression models did not find any association between any NSAID use, NSAID use before or after AD onset, or duration of NSAID use and participant survival. The conclusion of this project is that NSAIDs do

not affect AD progression or survival rates of persons with AD. These results are discussed within the scope of the current literature.

(118 pages)

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## CHAPTER I

### PROBLEM STATEMENT

Alzheimer's disease (AD) is a devastating neurodegenerative disease that affects millions of individuals worldwide. The majority of individuals with this disorder have an onset after the age of 65, although there are early onset forms that can begin at a much earlier age (Beyer, Lao, Latorre, & Ariza, 2005). AD is characterized by progressive impairment in memory and other cognitive domains, such as executive function, attention, and language. The course of the disease is also characterized by impairments in behavioral and functional abilities, and eventually leads to incapacity and death. There is no treatment for AD, only palliative care for symptom reduction and management. As one of the most common types of dementia in late-life, AD places significant economic and emotional burden on caregivers and society. Currently, AD is the third most costly disease in the United States, after cancer and cardiovascular disease (Ernst & Hay, 1994; Meek, McKeithan, Schumock, & Schumock, 1998).

Reducing the prevalence of AD would decrease personal and societal burden, because individuals with AD and their caregivers would be relieved of the great emotional and economic costs associated with treating and managing the symptoms of this disorder. However, because there are no available means of prevention, reducing the degree of disability among individuals already diagnosed with AD could also have enormous impact. Studies show that treating individuals in the early stages of AD is half as expensive as treating individuals in the late stages of AD (Moore, Zhu, & Clipp, 2001). In addition, studies show that decreasing the rate of disease progression delays

institutionalization and mortality, and can increase the quality of life in both individuals with AD and their caregivers (Meek et al., 1998).

Research identifies several contributing factors to the etiology of AD, primarily, the development of amyloid plaques and neurofibrillary tangles (NFT) in the brain. Amyloid plaques are extracellular substances formed between neurons by the deposition of beta-amyloid, remnants of other proteins, microglial cells, and other cellular material. NFTs are intracellular collections of twisted proteins that affect neural microtubules, the internal structures that maintain cellular integrity and aid in cellular transport. Together, these two processes are hypothesized to disrupt neuronal communication and synaptic function, and lead to neuronal death. In fact, research indicates that examining the presence of amyloid plaques and NFT postmortem can give an accurate diagnosis of AD 85% of the time without previous knowledge of dementia status (Andreasen et al., 2001; Hulstaert et al., 1999).

Many experimental compounds that directly target amyloid plaques and NFTs are under development to treat or prevent AD. However, compounds that decrease the accumulation of plaques and NFTs have only had marginal success, suggesting that there are also other factors associated with the disease (Breitner, 1996). These therapies have also been complicated by serious side effects such as increased risk of encephalitis and brain hemorrhaging (Gofii & Sigurdsson, 2005). Therefore, although amyloid plaques and NFTs are hypothesized to be the main contributing factors to AD, other treatments targeting other causes of AD are also being pursued.

An additional contributing factor to AD pathology is neuroinflammation, the body's natural inflammatory response to damage to the brain. Amyloid plaque

deposition and the formation of NFTs have been shown to trigger inflammatory responses within the brain. Under most conditions, inflammatory responses are beneficial, due to the activation of microglial cells that remove dead or dying neurons and waste products that may interrupt cellular functions. However, with chronic neuroinflammation, which is hypothesized to occur in AD, microglial response becomes over-expressed, attacking healthy neural tissue and contributing to neurotoxicity (Breitner, 1996; McGeer & McGeer, 2004; Walker & Lue, 2005; Wood, 2003). Microglial overexpression is also theorized to contribute to greater *tau* phosphorylation, resulting in the weakening of the microtubules within neurons and the eventual formation of neurofibrillary tangles and cell death (Mrak & Griffin, 2005). Because it has been shown that neuroinflammation promotes beta amyloid deposition and the formation of NFTs, it has been theorized that reducing brain inflammation may also reduce the neurotoxic elements that underlie AD pathology.

Non-steroidal anti-inflammatory drugs (NSAIDS) are analgesic, anti-inflammatory agents that have been shown to decrease inflammation of tissue, including tissue within the brain (Breitner, 1996; Zandi & Breitner, 2001). Because of their anti-inflammatory effects in the brain, NSAIDS have been thoroughly researched as a potential protective agent against AD. Several observational studies suggest that NSAIDS, if taken for long enough periods of time, may be effective in decreasing rates of incident AD (Breitner, 1996; McGeer, McGeer, Rogers, & Sibley, 1990; Stewart, Kawas, Corrada, & Metter, 1997; Zandi & Breitner, 2001). Substantial research suggests that the biological agents associated with AD onset, such as amyloid plaques and NFT, are also associated with the worsening of AD symptoms, both in animal models (Murphy

et al., 2007) and humans with AD (Augustinack, Schneider, Mandelkow, & Hyman, 2002; Haroutunian, Davies, Vianna, Buxbaum, & Purohit, 2007). Therefore, it is plausible that NSAIDS may not only be effective at decreasing incident rates of AD, but also at slowing the progression of AD after its onset. Factors that slow the rate of AD progression may be helpful in reducing the severity of cognitive and functional disability, and in promoting higher levels of functioning over the course of the illness. Although such treatments may not lead to a cure, they may be effective in reducing the emotional cost and burden for patients and their caregivers.

There have been few studies examining the effects of NSAIDS on the progression of cognitive and functional impairment in individuals diagnosed with AD. A small number of double-blind, randomized, controlled, treatment (RCT) studies examining the use of NSAIDS as a treatment of AD show that treatment groups score no higher on outcome scores of cognitive ability than placebo controls. However, an important limitation of these studies is the short time period of NSAID treatment, generally no longer than one year. The duration of NSAID use may be a critical factor, because retrospective longitudinal studies suggest that the efficacy of NSAIDS as a neuroprotective agent occurs only after prolonged periods of NSAID use (Hayden et al., 2007). In fact, a consistent finding in the field suggests a minimum duration of NSAID use of two years is necessary for a neuroprotective effect (Breitner, 1996). Extrapolating from these findings, one may hypothesize that the time requirement necessary for NSAID use to affect the trajectory of AD progression may be just as long, if not longer. In addition, the RCTs conducted provide no information regarding the history of NSAID use, once again ignoring the possibility that long exposure to NSAID use may have a

protective effect against AD progression. Finally, these studies only examined the effect of NSAID use on one aspect of AD progression, cognitive decline, but did not examine the effects of NSAID use on other indicators of disease progression, such as functional ability and survival duration.

In this project I examined the effects of NSAID use on the rate of dementia progression in a population-based sample of elderly individuals diagnosed with AD. Specifically, I examined the effects of NSAID use on the rate of cognitive and functional decline and survival duration in AD. Characteristics of NSAID use included the initiation of use relative to dementia onset and the duration of use.

## CHAPTER II

### LITERATURE REVIEW

#### **Introduction**

Alzheimer's disease is a progressive, degenerative brain disease that is characterized by declining memory and cognitive abilities, onset of behavioral and psychiatric symptoms, and a decline in functional abilities (Cummings, 2005). Currently, AD is estimated to affect approximately 4.5 million individuals within the United States (U.S.) alone, with this number estimated to rise to approximately 13.2 million by the year 2050 (Herbert, Scheer, Bienias, Bennett, & Evans, 2003). AD is the third most expensive disease to treat in the U.S., costing the U.S. economy approximately \$100 billion annually in direct and indirect costs (Ernst & Hay, 1994). For families, the total annual cost associated with AD is estimated at \$77,000. The cost of living with AD is more expensive than the costs associated with a physical disability (Schulz, Obrien, Bookwala, & Fleissner, 1995). In the late 1990s, AD ranked fourth among the leading causes of death within the U.S. (Meek et al., 1998).

The social and emotional costs of AD do not solely affect individuals diagnosed with the disorder. In recent years, research has focused on the emotional, physical, and economic impact on individuals who care for persons with AD. Several studies have suggested that caregivers of individuals diagnosed with AD experience more stress and have poorer levels of overall physical health than age-matched controls (Aguglia, Onor, Trevisiol, Saina, & Maso, 2004; González-Salvador, Arango, Lyketsos, & Barba, 1999).

Because the number of persons with AD increases exponentially with age, it has been suggested that even small changes in the prevalence and incidence rates of AD can have great impact on individuals and society as a whole (Brookmeyer, Carada, Curriero, & Kawas, 2002). For example, it has been suggested that increasing the onset of AD by only 5 years would decrease prevalence rates by 50% (Brookmeyer et al., 2002). In addition, reducing the rate of cognitive decline in individuals with AD can have great emotional and economic benefit, as individuals in the earlier stages of the disease are more capable of carrying out basic activities of living (Ory, Hoffman, Yee, Tennstedt, & Schultz, 1999). At least one study has shown that the costs of caring for individuals with AD doubles from the mild to moderate stages of the disease, and once again from the moderate to severe stages (Moore et al., 2001). One study suggests that even a small reduction of disability could save an estimated \$1,411 per year in medical costs and \$2,718 in unpaid care giving costs (Zhu et al., 2006). Clearly, the emotional, social, and economic costs associated with AD are widespread, making the treatment and prevention of this condition an urgent public health priority.

### **Contributory Factors to the Etiology of AD**

Although there is no concrete evidence as to what specifically causes the dementia in AD, three biological mechanisms have been implicated as important contributing factors: (a) the development and accumulation of amyloid plaques, (b) the creation of neurofibrillary tangles (NFT), and (c) neuroinflammation. This section will discuss how these three mechanisms contribute to AD pathology in the brain.



### **Amyloid Plaques and Neurofibrillary Tangles**

Amyloid plaques are nonsoluble deposits of a combination of beta-amyloid protein, other unspecified proteins, and accumulated microglia. Beta-amyloid is a protein that is cleaved from a larger protein named amyloid precursor protein (APP). Depending on the manner in which the protein is cleaved, significant amounts of the protein can build up over time. Studies have shown that genes involved in both the type of APP that is generated and the type of enzymes that cleave APP can influence the presence of amyloid plaques (Bird, 2008; Cruts & Broeckhoven, 1998). Studies have also shown that the amyloid processes or plaques interrupt cellular communication, which may eventually lead to neuronal cell death (Maccioni, Leonel, Fernández, & Kuljis, 2009).

NFTs are accumulations of protein that occur within microtubules, the cellular structures within neurons that are responsible for the transportation of substances necessary for cell growth, repair, and function. The microtubules within neurons are reinforced with a special protein called *tau*. The strength of this protein and its ability to stabilize microtubules rises from the number of phosphate molecules that surround it. However, in AD abnormal amounts of phosphate molecules bind to *tau*, leading it to disengage from the microtubule and bind with other *tau* molecules. This both weakens microtubules within neurons and also creates abnormal accumulations of *tau* molecules, which are toxic to the cell (Bramblett et al., 1993; Sengupta et al., 1998). Abnormal phosphorylation of *tau* molecules has been shown to play a major role in the accumulation of NFTs, and compounds that inhibit this process have been shown to decrease the amount of cellular loss in AD (Li, Liu, Barger, & Griffin, 2003b).

Abnormally high levels of unattached *tau* also inhibit axonal transport in cells, disrupting cellular communication (Tatebayashi, Haque, Tung, Iqbal, & Grundke-Iqbal, 2004).

Together, studies have shown that amyloid plaques and NFTs are highly diagnostic for AD, with some studies suggesting that these two biomarkers can provide a clinically accurate diagnosis of AD 85% of the time without foreknowledge of dementia status (Andreasen et al., 2001; Hulstaert et al., 1999). Although it is hypothesized that these two processes contribute to the neurobiological changes involved in AD, current research is unclear which of these two processes is primarily responsible for the pathology of AD. Within the past several years, the question of which contributes more to AD pathology, amyloid plaques or NFTs, has been a heated debate among researchers. Current research suggests, however, that there is an interrelationship between the two, with beta amyloid contributing to the accumulation of both plaques and tangles (Hardy & Selko, 2002). Studies have shown that this occurs because of both the direct and indirect effects of beta-amyloid on *tau* phosphorylation and NFT formation, in animal models and research with human subjects (Lewis et al., 2001; Oddo et al., 2003). For example, in animal models, Oddo et al. (2003) found that when a beta-amyloid antibody was administered into the hippocampus of one hemisphere in mice, not only were beta amyloid levels reduced, but abnormal levels of *tau* within the cell bodies and dendrites in the hippocampal neurons were reduced as well. In the contra-lateral hemisphere that did not receive the amyloid antibody, no reductions in abnormal *tau* levels were observed (Oddo et al., 2003). In another study conducted by Oddo, Billings, Kesslak, Cribbs, and LaFerla (2004), a triple transgenic model of AD was created, using mutant beta-amyloid, presenilin-1 and tauP301L genes. In their model, which closely resembles the trajectory

of AD pathology in humans, Oddo et al. (2004) discovered that beta-amyloid deposition develops prior to the *tau* pathology that contributes to NFT formation.

In human subjects, studies have also found that amyloid plaques can increase *tau* phosphorylation, which ultimately increases *tau* aggregation, mislocalization, and accumulation (Blurton-Jones & LaFerla, 2006). As mentioned previously, *tau* phosphorylation weakens neural microtubules and contributes to the creation of NFTs. In animal models, studies have shown that *tau* exposed to beta-amyloid increases its phosphorylation both in *in vitro* and *in vivo* studies (Alvarez, Toro, Caceres, & Maccioni, 1999; Busciglio, Lorenzo, Yeh, & Yanker, 1995; Hwang et al., 2004; Puig et al., 2004; Takashima, Noguchi, Sato, Hoshino, & Imahori, 1993). Studies have also shown that beta-amyloid induces microglial activation and the release of inflammatory cytokines, proteins involved in cellular communication, which also may accelerate *tau* pathology and NFT formation (Li et al., 2003a; Quintanilla, Orellana, González-Billaut, & Maccioni, 2004; Tan, Beiser, & Vasan, 2008).

Beta-amyloid accumulation can also affect *tau* pathology through proteasomal dysfunction and by disrupting axonal transport. Proteasomal dysfunction refers to the creation of misfolded proteins through dysfunctional transcription factors, the process by which genetic information is extracted from DNA to create the proper proteins to synthesize materials within the body. Dysfunction of this system has been shown to play a role in a variety of neurodegenerative conditions, such as Huntington's disease, Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease, prion diseases, and AD (Blurton-Jones & LaFerla, 2006). Proteasomal dysfunction is accelerated by beta-amyloid pathology, and also contributes to the build-up of *tau* accumulations within

neural cells (Blurton-Jones & Laferla, 2006; Oddo et al., 2004). Axonal transport is the process by which materials such as lipids, proteins, and other materials necessary for cellular function travel to or from the body of the neuron. The process is negatively affected by both beta-amyloid and *tau* accumulation (Blurton-Jones & Laferla, 2006). Although the degree to which beta-amyloid plaques and NFT each negatively affects axonal transport is currently debated, recent *in vivo* evidence supports the hypothesis that beta-amyloid-induced axonal transport deficits leads to the mislocalization of *tau*, the prominent feature of NFTs (Lewis et al., 2001). In addition, studies have shown that beta-amyloid axonal transport deficits have led to increases in NFT pathology. By contrast, axonal transport deficits caused by *tau* pathology have not significantly contributed to beta-amyloid pathology (Ishihara et al., 1999; Zhang et al., 2004).

### **Neuroinflammation**

In addition to the effects of beta-amyloid and *tau* pathology in AD, research suggests that other factors contribute to the overall pathophysiology of AD. One prominent process believed to contribute to neurodegeneration in AD is that of neuroinflammation. Amyloid plaques have been shown to trigger inflammatory responses within the brain, including the activation of microglial cells. Microglial cells are a type of glial cell (nonneuronal cell) within the central nervous system (CNS) that aid in the recognition and consumption of antigens and neuronal waste products and in repairing damaged neurons. These cells are highly abundant within the CNS, and constitute approximately 20% of all glial cells (Wood, 2003). Under normal circumstances, microglia functions include providing cellular maintenance and clean-up

of cellular debris, as well as serving critical roles in defending neurons from invading pathogens within the brain (Wood, 2003). However, substantial evidence suggests that when the microglial response exceeds general “housekeeping” functions, and does not return to baseline levels, chronic, excessive, and continuous microglial activity can be toxic to the human brain. This toxicity creates a cycle that leads to a sustained, chronic state of inflammation (McGeer & McGeer, 2004; Walker & Lue, 2005; Wood, 2003).

Studies of brain tissue from individuals with AD have shown increased rates of microglial release and activation. For example, several studies conducted at autopsy have discovered significantly more widespread activation of microglia in the cortical areas in AD patients than in similar areas among normal, age-matched controls (Akiyama, Kawamata, Dedhar, & McGreer, 1991; Arends, Duyckaerts, Rosemuller, Eikelenboom, & Hauw, 2000; Griffin, Sheng, Roberts, & Mrak, 1995; Itagaki, McGreer, & Akiyama, 1988). Complement fragments, a prominent part of the inflammatory response cycle, are involved in stimulating microglial release and are also found in abundance in the AD brain, but are nonexistent in normal controls (McGeer & McGeer, 2001; Neuroinflammation Working Group, 2000). In addition, at least one study has shown that microglial activation in the cortex occurs early in the disease process, setting the stage for a cascade of other events that all contribute to the neuropathology seen in AD (Cagnin et al., 2001). The heightened activity of microglia is toxic to the human brain, the mechanism of which is hypothesized to occur through one of three primary processes: (a) increased beta-amyloid and *tau* depositions through the production of additional APP, (b) oxidative stress, and (c) microglial effect on contributory cellular processes.

Many researchers hypothesize that sustained microglial activation is an essential element to the progressive pathological cascade of plaque formation (Griffin et al., 1995). This is thought to occur through the genesis of additional APP. As discussed previously, beta-amyloid is cleaved from a larger protein called APP, and greater amounts of APP within the CNS may ultimately contribute to higher levels of beta-amyloid plaques (Frackowiak et al., 1992; Mackenzie, Hau, & Munoz, 1995). Studies have shown that microglial activation is a major source of APP production and release, which in turn may contribute to greater amyloid plaque formation (Frackowiak et al., 1992; Mackenzie et al., 1995; Perlmutter, Barron, & Chul, 1990).

Compounds that inhibit microglial activation have been found to be moderately effective in reducing the amyloid plaques and NFTs found in animal models of AD, thus providing evidence of the interactions between microglial activity and AD lesions (Hensley et al., 2000; Mogi et al., 2000; Pulliam et al., 2001; Tikka, Fiebich, Goldsteins, Keinanen, & Koistinaho, 2001). Microglial release and other neuroinflammatory processes are also associated with increased *tau* phosphorylation, which contributes to NFT formation in AD (Mrak & Griffin, 2005).

Neuroinflammation has also been shown to contribute to AD pathology through excessive generation of oxidative stress (McGeer & McGeer, 2004). Oxidation is the natural outcome that occurs in the human body through the process of oxygen and cellular metabolism. However, when this natural process occurs at abnormally high levels, or is not able to be neutralized by other substances, it becomes toxic to the brain and other organs via the creation of oxygen free radicals. Oxidative stress has been shown by multiple studies to be a contributing factor to the cellular processes that

contribute to AD pathology (Banat, Gehrmann, Schubert, & Kreutzberg, 1993; Colton & Gilbert, 1987; Corradin, Manuël, Donini, Quattrocchi, & Ricciardi-Castagnoli, 1993).

Microglia activation contributes to excessive oxidative stress; in fact, the activation of microglia is among the primary sources of free radical production in the CNS (McGeer & McGeer, 2004).

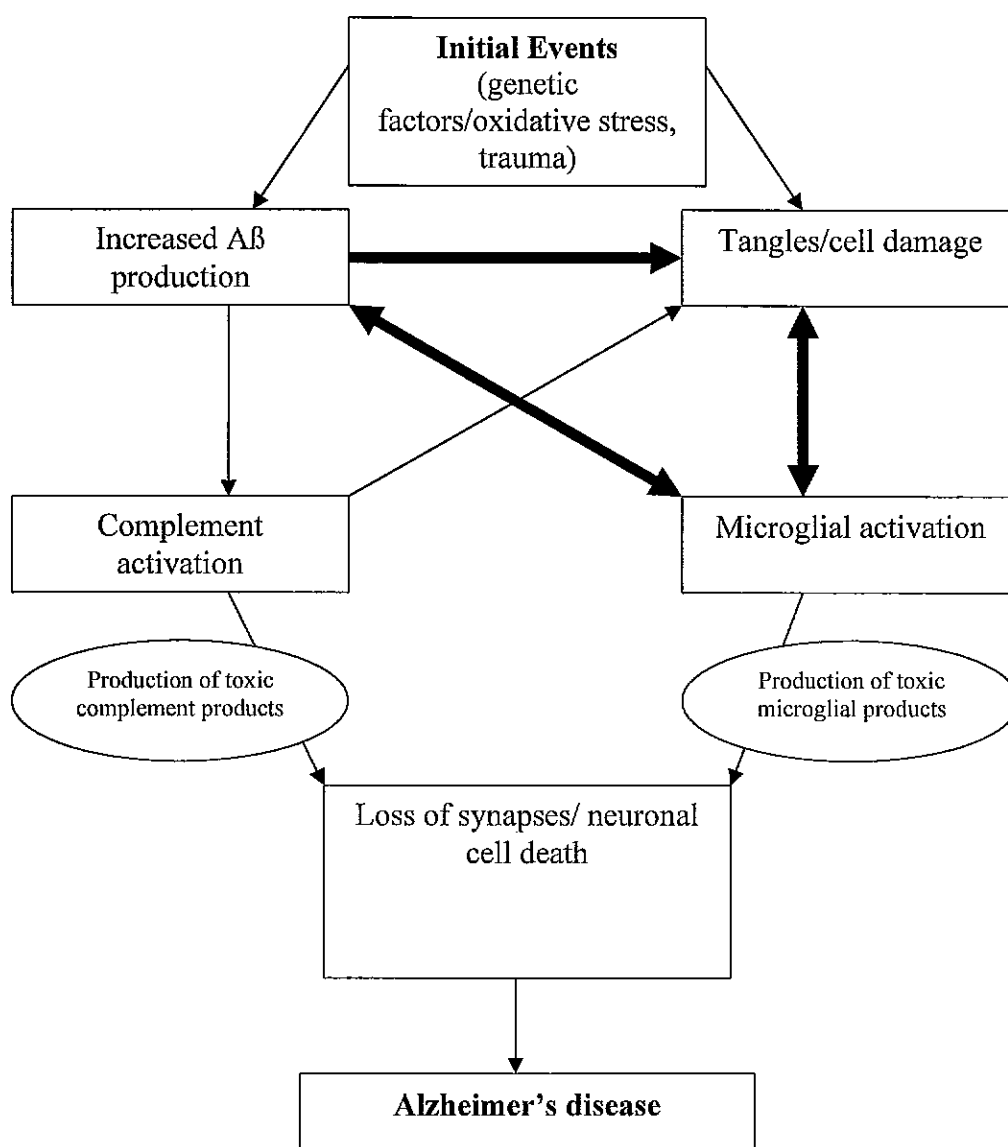
Lastly, one additional mechanism by which neuroinflammation contributes to the pathology of AD is through the Classical Complement Pathway (CCP). The CCP is the part of the body's immune system that is designed to identify, destroy, and relieve the body of foreign substances, and does so by releasing the biological agents responsible for destroying foreign material. However, one problem with CCP activation is that if host cells have insufficient protection against the agents released by the CCP, then damage may come to that host cell through a process called "bystander lysis."

The CCP is activated as part of the neurophysiological response to the deposition of beta-amyloid protein and plaques. Normally the CCP would consume invading organisms, however, because there are no foreign substances to consume, the agents released by the CCP begin to attack the host neuron, which leads to cellular damage and death (McGeer & McGeer, 2004).

The process by which amyloid plaques, NFT, and neuroinflammation contribute to AD pathology is complex. Figure 1 depicts the dynamics of these three elements, and how together they contribute to create AD pathology.

### **Nonsteroidal Anti-Inflammatory Drugs (NAIDS) and AD Prevention**

NSAIDS are medications that have analgesic and anti-inflammatory effects on the



*Figure 1.* The hypothetical interactions of inflammatory-associated events in the causation of Alzheimer's disease (complement and microglial activation represent inflammatory processes (reproduced with permission from Humana Press Publishers; Wood, 2003).



human body, and are the most frequently prescribed drugs for treating fever, pain, and inflammation (Gasparini, Ongini, & Wenk, 2004; Kelley, Harris, Ruddy, & Sledge, 1989). Studies have shown that these drugs reduce the body's natural inflammatory response in a variety of different ways. One of the primary ways in which NSAIDS reduce inflammation is by blocking the cyclooxygenase (COX) enzyme, which is the primary regulatory enzyme of proinflammatory systems within the body (Gasparini et al., 2004; Vane, 1971). There are several different COX enzymes within the human body, with COX-1 being the primary agent involved in normal "housekeeping" activities (i.e., cellular nutrition, clean-up of cellular debris), and COX-2 being the primary agent involved in phagocytotic and repair functions (Gasparini et al., 2004).

Studies of human brain tissue show that when COX enzyme expression is blocked, the neuroinflammation associated with brain injury is reduced (Halliday, Robinson, Shepherd, & Kril, 2000; Sairanen, Ristimäki, & Karjalainen-Lindsberg, 1998). There is also considerable evidence from both *in vivo* and *in vitro* studies that suggests NSAIDS decrease the inflammatory responses induced by glial cells and microglial activation, both potent contributors to AD pathology (see Halliday et al., 2000 for complete review). Evidence from animal studies also suggests that NSAID use may inhibit the inflammatory responses that are *specifically* associated with amyloid plaques and beta-amyloid deposition, which, as discussed previously, contribute to the chronic inflammatory response seen in AD (Netland, Newton, Majocha, & Tate, 1998; Scali et al., 2000).

Because of the suppressing effects NSAIDS have on neuroinflammation, and the effect that neuroinflammation has on the aging brain, it has been hypothesized that

NSAIDS may have preventative effects on diseases such as AD. This hypothesis arose largely due to early findings that suggested that individuals diagnosed with rheumatoid arthritis (RA) had lower rates of AD and other types of dementia than individuals without RA. RA is an autoimmune disease in which the body's immune system attacks the joints of the body causing inflammation and pain. To help alleviate the pain and inflammation associated with RA, anti-inflammatory agents are often prescribed and taken for prolonged periods of time (Kelley et al., 1989). Retrospective observational studies have shown that RA patients treated with NSAIDs for long periods of time have a decreased risk of developing AD, and that concordance rates between RA and AD diagnosis are lower than one would expect for the two individual probabilities of each disease occurring separately. For example, in a group of 7,490 discharged elderly patients, McGeer et al. (1990) found that the co-morbidity of AD and RA was only .039%. According to Breitner (1996), this is approximately 6 to 10 times lower than what one would expect from the individual incidence rates of the two diseases. Additionally, within their study, 6 of the 22 participants (> 25%) who were diagnosed with both AD and RA were only diagnosed with AD several years after having discontinued their NSAID use. According to McGeer et al. (1990), this likely gave additional time for AD related neuropathology, promoted by inflammation, to take effect. Also, among the 22 individuals diagnosed with AD and RA, 21 of the 22 (>95%) all had a history of NSAID use (McGeer et al., 1990). This raised the possibility that the unexpectedly low concordance rates for AD and RA may be due to the long and persistent exposure to NSAIDS among individuals with RA (McGeer et al., 1990).

In addition, in a review of 17 epidemiological studies in nine different countries, McGeer, Schulzer, and McGreer (1996) examined the relationship between arthritis, anti-inflammatory medication use, and AD. They concluded that NSAID use may have a protective effect against developing AD. Specifically, they reviewed 14 case-control studies, and found that the average odds ratio for AD associated with NSAID treatment was 0.569 ( $p < .05$ ), suggesting that individuals taking NSAID medications were approximately 50% less likely to develop AD than individuals not taking NSAID medication (McGeer et al., 1996). In their review, McGeer et al. (1996) also discussed three population-based studies, the results of which “strongly supported the results of case-control studies.”

The purported link between NSAID use and prevention of AD has been extensively studied, with the vast majority of studies concluding that NSAIDs are effective at delaying or preventing AD. Etminan, Gill, and Samii (2003), systematically reviewed nine studies, with over 14,500 subjects (six cohort studies and three case-control studies), that examined the effects of NSAID use on specific AD diagnosis (other forms of dementia were excluded). In their review, Etminan and colleagues found that NSAID users were less likely to be diagnosed than non-NSAID users, but only if NSAID use was greater than 2 years. In another study, Szekely and colleagues (2004) conducted a meta-analytic review of NSAID use and development of AD. The results were largely consistent with those reviewed by Etminan et al. (2003). Their study revealed an odds ratio of 0.51 (95% CI = 0.40-0.66,  $p < 0.001$ ) for developing AD in retrospective studies, and a Relative Risk Ratio (RRR) of 0.42 (95% CI = 0.26-0.66,  $p < 0.001$ ) in prospective studies, but once again only if NSAID use was greater than 2 years. This suggested that

in both types of studies, individuals who used NSAIDs longer than 2 years were approximately 50% less likely to develop AD than nonusers. More recently, in a review conducted by De Craen, Gussekloo, Vrijssen, and Westendorp (2005), NSAID use also was found to significantly prevent AD. However, in their review, de Craen and colleagues found differences between the RRRs between prevalent and incident cases of AD (0.51 and 0.79, respectively), a reduction of risk of 50% in prevalent samples but only 20% in incident samples. De Craen and colleagues concluded that these differences may be partly due to recall and prescription bias in those with prevalent AD. However, they offered no evidence regarding the disparity between subject and informant reports of medication use, nor regarding NSAID termination in individuals with AD opposed to individuals without AD. In addition, many of the studies reviewed relied on surrogate informants and the direct examination of medicine containers and medical records in the data-gathering process, therefore decreasing the extent to which the study results may be due to recall bias (Szekely et al., 2008). Finally, in this review, AD was not the only dependent variable examined. In 6 of the 21 studies surveyed, over 25% of the cases were diagnosed with some other form of dementia. This inclusion criterion differs from other studies that only examined AD. Studies have shown that different types of dementia may differ significantly in neuropathology, trajectory, and causes (Amar & Wilcock, 1996); thus, the effects of NSAIDS in dementia may differ by dementia type.

In summary, the results of studies examining the relationship between NSAID use and AD strongly suggest that NSAID use has at least some prophylactic effect on AD (In't Veld, Ruitenburg, & Hofman, 2001; Jonker, Comijs, & Smit, 2003; McGeer & McGeer, 2004). Research has also suggested that there are other factors to consider when

interpreting the relationship between NSAID use and AD. One of the most important factors to consider in the relationship between these two variables appears to be the duration of NSAID use. As can be seen from the literature presented above, the majority of studies report greater reduction in AD risks for individuals who have consistently taken NSAIDS for at least 2 years. In addition, in an editorial composed by Breitner and Zandi (2001), they claim that there is also a general consensus in the field that NSAID exposure of at least two years is necessary for the prophylactic effects of NSAIDS on AD. Another important factor to consider is the type of NSAID used and the specific genotype of individuals at risk, particularly for genes that have been associated with AD pathology, such as apolipoprotein E (*APOE*), as there is some evidence that greater benefit is seen among individual NSAID users if they are also carriers of the E4 allele at *APOE* as compared to noncarriers (Szekely et al., 2008).

### **NSAID Use and Cognitive Decline**

#### **after the Onset of AD**

Despite the theoretical basis supporting the role of NSAIDs in reducing neuroinflammation in AD, and research suggesting that chronic NSAID use slows cognitive decline in elderly individuals (Fotuhi et al., 2008; Rozzini, Ferrucci, Losonczy, Havlik, & Guralnik, 1996), few studies have been conducted examining how NSAID use impacts the rate of dementia progression after AD onset. The results from these studies have been mixed, and are discussed below.

In a small RCT Rogers et al. (1993) examined 28 individuals in the mild to moderate stages of AD. They divided their sample into treatment ( $n = 14$ ) and placebo

( $n = 14$ ) groups, with the placebo group matched to the treatment group on age, gender, and baseline cognitive testing scores. The treatment group was administered indomethacin, three times a day. Indomethacin is an NSAID with well-documented data for its safety and anti-inflammatory effects. The dose was based on the participant's weight. The two groups were administered cognitive tests including the Mini-Mental State Exam (MMSE), Alzheimer's Disease Assessment Scale (ADAS), Boston Naming Test (BNT), and the Token Test (TK), once at study baseline before the inception of treatment, and once again 6 months after baseline testing. Overall, the treatment group improved in cognitive performance across the four tests an average of 1.3% ( $\pm 1.8\%$ ) points within the 6 months of treatment, whereas the placebo group declined in performance across the four tests at an average of 8.4% ( $\pm 2.3\%$ ), indicating that indomethacin was effective in decreasing the amount of cognitive decline for AD participants within their study.

In an observational study examining the effects of NSAIDS on cognitive decline among individuals with AD, Rich et al. (1995) examined the differences on cognitive testing between AD patients who had ( $n = 32$ ) and had not ( $n = 177$ ) a prior history of NSAID use. The two groups differed in time since diagnosis of AD, with the group of non-NSAID users having a longer duration of AD illness than the NSAID group. However, after controlling for the time since AD diagnosis, the NSAID group performed better than the non-NSAID group on MMSE scores ( $p = .01$ ), BNT scores ( $p = .04$ ), and on the delayed recall portion of the Benton Visual Retention Test (BVRT;  $p = .02$ ). Rich and colleagues also examined the effects of NSAID use on cognitive decline within their sample by examining cognitive testing scores one year after baseline scores. After again

co-varying for disease duration, the NSAID group showed significantly less decline on MMSE and BNT scores, but not BVRT scores (Rich et al., 1995). The differences on these specific neuropsychological tests are noteworthy, as MMSE scores are correlated with AD severity, and BNT scores are a measure of confrontational naming, an ability that declines early and precipitously in the disease trajectory of AD (Rebock, Brandt, & Folstein, 1990).

Despite these two studies that have shown beneficial effects of NSAID use on cognitive decline of participants with AD, clinical trials of NSAID medications on the treatment of AD have failed to produce positive results. Three main RCT studies are frequently cited within the literature that have examined the results of Rofecoxib, Naproxen, and Diclofenac on the cognitive trajectories of individuals diagnosed with AD. In the first, Reines et al. (2004) examined the effects of Rofecoxib on 692 individuals diagnosed with mild to moderate AD in a one-year randomized, double-blinded, controlled study. In their study, the treatment group received 25 milligrams of Rofecoxib and the control group received a placebo. Rofecoxib is an anti-inflammatory medication that selectively inhibits the COX-2 prostaglandins responsible for pain and inflammation, as opposed to traditional NSAIDS that also block COX-1 prostaglandins. The resulting difference of effects is that COX-2 inhibitors are purported to lack the gastrointestinal side-effects associated with traditional NSAIDS (Reines et al., 2004). This is of clinical value because past studies have demonstrated that such side effects have contributed to high drop-out rates in RCTs examining NSAID use and rate of cognitive decline in AD (Reines et al., 2004). Study participants were assessed using the cognitive subscale of the AD assessment scale (ADAS-cog) and the Clinician's Interview Based Impression of

Change with caregiver input (CIBIC+). Both instruments are routinely used in the assessment of AD and AD progression in clinical trials (Reines et al., 2004). The participants were given each test at baseline and once again after 12 months of drug or placebo treatment. Following the 12 months of treatment, the results of their study revealed no significant differences on either the ADAS-cog or CIBIC+ between the treatment and control groups.

In a study conducted by Aisen et al. (2003), the effects of Rofecoxib and Naproxen on cognitive decline were examined within a sample of subjects with mild to moderate AD. In their study, the overall sample ( $n = 351$ ) was divided into three groups that consisted of one group being treated with Rofecoxib, one group being treated with Naproxen, and one group receiving a placebo. While both Naproxen and Rofecoxib are categorized as NSAIDs, Naproxen falls within the category of a “traditional NSAID” and therefore its use may be associated with the gastrointestinal side effects of other traditional NSAIDs. Similar to the study conducted by Reines and colleagues described previously, each group was administered the ADAS-cog once at baseline and again after a 1-year treatment period. Their results suggested that neither Rofecoxib nor Naproxen had any significant effects on cognitive decline compared to the placebo group over a 1-year treatment period (Aisen et al., 2003).

In a study conducted by Scharf, Mander, Ugoni, Vajda, and Christophidis (1999), the effects of Diclofenac were examined on AD progression in a group of 41 patients with mild to moderate AD. Diclofenac is also categorized as a “traditional” NSAID, similar to Naproxen, and inhibits both COX I and II. Similar to the outcome studies discussed above, Diclofenac did not significantly alter the course of cognitive decline in a



sample of individuals diagnosed with AD following 6 months of NSAID treatment (Scharf et al., 1999). It is important to note, however, that Scharf and colleagues did note a nonsignificant trend in the placebo group to perform worse on objective measures of cognitive ability compared to the treatment group. In fact, Scharf and colleagues argued that perhaps with a larger sample, significant values could have been obtained, and that further studies with larger sample sizes and greater power are warranted (Scharf et al., 1999).

Although the studies described above have not shown beneficial effects of NSAID medication on the trajectory of cognitive decline in AD, there are several limitations that warrant discussion. One main criticism is the short time period in which the studies were carried out. As discussed earlier, research on the prophylactic effects of NSAIDS on AD suggest that NSAIDS are only effective if taken for extended periods of time. In fact, as mentioned previously, several studies and researchers within the field suggest that the beneficial effects of NSAIDS on delaying the progression of AD pathology only occurs if the medications are taken for at least 2 years (Breitner & Zandi, 2001). In addition, current research suggests that the beneficial effects of NSAIDS on postponing AD may only occur early in the disease process, or before the onset of cognitive symptoms. Although it is difficult to ascertain when the pathology of AD begins (mounting research suggests that AD pathology may begin much earlier in life than the onset of AD symptoms; Reiman, 2007), it has been hypothesized that there is a purported “critical window” in which NSAIDS must be taken in order to delay or prevent the symptoms of AD from occurring (Zandi & Breitner, 2001). This critical window is hypothesized to exist in the latent stages of the disease, where, although the pathology of

AD may have already begun, the damage in the brain is insufficient to produce the actual cognitive symptoms associated with AD (Zandi & Breitner, 2001). If this hypothesis proposed by Zandi and Breitner is correct, then the clinical trials discussed above would not be expected to reduce the cognitive deterioration seen in AD because the pathology associated with the disease has progressed beyond the point where intervention can make a difference. It may be that for a beneficial effect of NSAIDs to be seen after the onset of AD requires an initiation of NSAID use before dementia criteria are met and continued for a duration of use of at least two years. Therefore, as proposed by Breitner and Zandi (2001), future studies examining the effects of NSAID use on AD progression should also interact NSAID use with age to examine any interactive effect between these two variables. In addition, as research has shown, the presence of the APOE  $\epsilon 4$  allele may modify the effect of NSAID use on AD progression (Szekely et al., 2008).

In summary, research suggests that delaying the progression of AD has many social, emotional, and economic benefits. One potential treatment to slow the progression of AD may be NSAID use. Several studies have been conducted examining the effects of NSAID use on the cognitive trajectory of AD, and have provided mixed results. These studies, however, may not have examined important variables, such as the initiation of use, duration of use, and the possible moderating effects of APOE genotype. In addition, studies examining the effects of NSAID use on AD progression have focused solely on cognitive decline, and have not considered other variables involved in the progression of AD, such as functional ability or survival duration.

In this study I will examine the relationship between NSAID use and dementia progression in individuals with AD. I will specifically examine whether initiation and

duration of NSAID use affect the rate of cognitive and functional decline and survival duration after the onset of dementia. Specific research questions are listed below:

1. Does any NSAID use taken during the course of dementia affect the rate of cognitive and functional decline and survival duration of individuals with AD?
2. Does the initiation of NSAID use, before or after dementia diagnosis, affect rate of cognitive and functional decline and survival duration in individuals with AD?
3. Does the duration of NSAID use affect the rate of cognitive and functional decline and survival duration in individuals with AD?
4. Is there any evidence of APOE  $\epsilon 4$  interaction with NSAID use on the rate of cognitive and functional decline and survival duration among individuals with AD?
5. For each of the research questions above, I will test for potential confounding factors, including age, duration of dementia, and gender. Furthermore, if the NSAID use affects the rate of dementia progression and survival duration, I will conduct an analysis with control medications (compounds taken for similar reasons of anti-inflammatory effects but that lack this property), to rule out the effects of other factors associated with the use of pain medications.

### CHAPTER III

#### METHODS

This project will utilize data from the Cache County Study on Memory, Health, and Aging (CCSMHA), a longitudinal population study on the memory, health, and aging process of elderly individuals residing in Cache County, Utah. The data to be used in this project consist of individuals with AD identified over four waves of dementia screening and assessment, and subsequent follow-up for up to 5 years in the Dementia Progression Study (DPS) from the CCSMHA. In this section, I will provide a broad overview of the study, providing information on the protocol used for identifying individuals with dementia.

#### **CCSMHA Dementia Screening and Assessment**

The CCSMHA has been ongoing since 1995, and has completed four waves of dementia screening and assessment, completed approximately every 3-4 years. In Wave 1, resident individuals residing in Cache County, Utah, aged 65 and older as of January 1<sup>st</sup>, 1995 ( $N = 5,677$ ; Breitner, 1996) were invited to undergo a multistage dementia screening and assessment protocol. Study participants were also asked about their medicine use and medical history. Cognitive screening consisted of a revised version of the Modified Mini-Mental State Exam (3MS; Teng & Chui, 1987). Individuals whose sensory and education adjusted screening scores fell below 87 out of 100, or who were selected as a “designated” subsample to complete all stages of screening and assessment, were then studied further using the Dementia Questionnaire (DQ), an informant-based

interview (Silverman, Breitner, Mohs, & Davis, 1986). The designated subsample was sampled according to an iterative process to match each identified case of AD according to age, gender, and APOE genotype. The results of the DQ were rated by a neuropsychologist in consultation with a senior geropsychiatrist and neuropsychologist. Elderly individuals who were given the rating of “dementia” or “significant cognitive decline” were then invited to undergo a comprehensive clinical assessment, conducted by a research nurse and neuropsychological technician. The nurse and neuropsychological technician administered a battery of neuropsychological tests and neurological exams that included the Consortium to Establish a Registry for AD (CERAD), a frequently utilized neuropsychological battery in assessing progression of AD within the elderly. Additionally, an informant named by the participant completed the Dementia Severity Rating Scale (DSRS; Clark & Ewbank, 1996), which identified the participants’ competence in the major functional and cognitive domains affected by dementia. Following the clinical visits, study participants were also administered the identical battery of neuropsychological tests in an 18-month follow-up visit.

Data collected from clinical assessment were then reviewed by a geropsychiatrist and neuropsychologist, who assigned preliminary diagnoses of dementia according to *Diagnostic and Statistical Manual of Mental Disorders* (3<sup>rd</sup> ed.; DSM-III-R; American Psychiatric Association, 1987) dementia criteria. Those not meeting dementia criteria were classified with other cognitive disorders or no impairment. Subjects diagnosed with dementia were then classified according to severity stages of dementia using the Clinical Dementia Rating Scale (CDR; Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1997). Age of dementia onset was assigned based on a chronology of symptoms as the

age at which individuals met DSM-III-R (APA, 1987) criteria for dementia.

Additionally, participants who were diagnosed with dementia or its prodrome were invited to undergo additional laboratory testing and neuroimaging using magnetic resonance imaging (MRI). Those with dementia diagnosis were also invited to have a geropsychiatric evaluation.

A final diagnosis of dementia was assigned after a review of all available information (clinical assessment, laboratory and neuroimaging information, and geropsychiatry evaluation) at consensus conferences consisting of experienced clinicians in geropsychiatry, neurology, and neuropsychology. A diagnosis of AD followed the criteria provided by the National Institute of Neurological and Communicative Disorders and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984). Diagnoses of other types of dementia followed other standard research protocol. All study procedures were identical in each wave, with the exception of a slight modification of screening cut-off scores in Waves 2, 3, and 4, and the elimination of the DQ in Waves 3 and 4. In these two waves, individuals who met the cut-off criteria for the 3MS were chosen to participate in the clinical visits as described above. Furthermore, Wave 4 MRI and laboratory testing were restricted to those whose diagnosis of dementia-type was unclear.

Following a diagnosis of dementia, participants were then followed at a 12-18 month visit to confirm their dementia diagnosis, and subsequently on a semiannual basis according to the protocol delineated in the DPS. The study procedures were similar to that of the clinical assessment in which measures of medications and medical history were completed.

## **Study Participants**

The participants in the present project include those who were diagnosed with AD following the CCSMHA methods as explained above. Following the first screening wave of the CCSMHA, 356 individuals were diagnosed with dementia, and were therefore labeled as “prevalent dementia” cases. Following Wave 2, 191 individuals were identified with dementia. In Waves 3 and 4, 394 individuals were identified with dementia, thus totaling 941 individuals identified with dementia following the four screening waves of the study, 356 prevalent cases and 585 incident cases. Of the 941 individuals identified with dementia, 572 (60.7%) were diagnosed with AD. Of these, 244 cases were prevalent cases whereas 328 were incident cases. The 328 incident cases comprise the sample of this study.

## **Study Measures**

### **Mini-Mental State Exam**

The MMSE test is often used as a screen for dementia and cognitive decline in elderly populations. The test includes questions and problems in a number of different areas, including psychomotor skills, memory, orientation, language use, comprehension, and constructional praxis. The test ranges in scores from 0-30, with scores 27-30 suggesting normal functioning, 20-26 suggesting mild dementia, 10-19 moderate dementia, and below 10 severe dementia, with low to very low scores correlating closely with the accurate diagnoses of dementia (Folstein, Folstein, & McHugh, 1975). The test

form used in the CCSMHA and DPS was the CERAD modified version (Welsh et al., 2004). A copy of the MMSE can be found in Appendix A of this project.

### **Clinical Dementia Rating Scale (CDR)**

The CDR is a scale that is used to rate dementia severity and functional outcomes in participants with dementia (Juva et al., 2006). The scale is completed during a semistructured interview administered by a nurse, and focuses on the participant's functional abilities in six different areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Scores in each of these areas may be combined to obtain a composite score on a 5-point scale, with values of 0 (*no cognitive impairment*), 0.5 (*questionable dementia*), 1 (*mild dementia*), 2 (*moderate dementia*), 3 (*severe dementia*), 4 (*profound dementia*), and 5 (*terminal dementia*). For this project, I summed the scores in each domain to use as a total CDR score, referred to as the CDR Sum of Boxes (CDR-SB) method, a method used by O'Bryant et al. (2008), utilizing a range of scores from 0-30. A copy of the CDR can be found in Appendix B of this project.

### **Survival Duration**

As part of ongoing surveillance of the CCSMHA, mortality was monitored by newspaper obituaries and by quarterly reports from the state of Utah Department of Vital Statistics. For each death, the date of the death was obtained, and survival duration will be calculated from the age of dementia onset to the date of death (in years).



### **Medication Questionnaire**

During each screening wave of the CCSMHA and continued in the DPS, participants were asked to show the interviewers all of the medications, ointments, and nutritional supplements they were currently taking. They were then asked if they suffered from a medical condition from a selected group of medical conditions (such as painful or inflammatory conditions, respiratory or gastrointestinal problems, and others). They were then asked if they used any medications that pertained to each grouped condition from an 8 x 11 printed drug card that listed various prescription and nonprescription medications commonly used to treat the conditions. Such questions were asked in the form of: "Have you used any of the medications on this card regularly, that is once a week for a month or longer, for any of the conditions that we just discussed or for any other reason?" Reported current and past medication use was then noted for its type, duration, amount, form, and reason for consumption in a medication booklet. Finally, participants were then asked once again for any prescription or nonprescription drug use for those conditions that were not listed on the 8 x 11 printed drug cards.

Type of medication use was then coded by a team of Quality Assurance (QA) technicians, using the Mosby coding system (Mosby's, 2007). Medications that resembled many of the effects of NSAIDS, such as analgesia and fever-reduction properties, but that lacked the neuroinflammatory effect of NSAID medications, were coded and available for use as the control group of medications in this project (i.e., Tylenol). The medication questionnaire was used in each wave of the CCSMHA and each visit of the DPS.

### Coding NSAID Use

To characterize NSAID use, certain aspects of use were important to capture, such as: (a) a participant *ever* using NSAIDs, (b) the *initiation* of NSAID use in relation to the onset of dementia, and (c) the *duration* of NSAID use. Every use of NSAID was coded positively if the use of any NSAID was taken for a minimum of at least once a week for a month or longer. This threshold has been used in other work from the Cache County Study (Hayden et al., 2007). To reflect initiation of use, I created a second variable that reflected the timing of NSAID use, before or after AD onset, or both before and after AD onset. This variable had four levels: (a) individuals who had never used NSAID medications, before or after dementia onset, (b) NSAID users prior to dementia onset only, (c) NSAID users after dementia onset only, and (d) NSAID users both before and after dementia onset.

Addressing issue number three required capturing NSAID exposure throughout the lifespan to capture the duration of lifetime NSAID use. Because NSAIDs are often taken in episodes, the age at which NSAID exposure began and the age at which NSAID exposure ended was determined as well as the total number of episodes. Exploratory analyses revealed that subjects often began use, stopped, and then resumed use years after initial use. Because it was not assumed that periods of no-use could be considered continuous, I derived the NSAID duration variable as a time-dependent variable, not a time-continuous variable. Although there were some reports of NSAID exposure in childhood and adolescence, their use was excluded due to potential recall bias and relevance to inflammatory processes in late-life. Thus, to be considered positive for exposure required any reported NSAID use after age 45.

### **Strategy to Address Inconsistent Reporting**

Because of the CCMS and DPS studies queried participants and caregivers at each wave and visit there were several opportunities for discrepant reporting due to recall bias of start and stop dates. Such discrepancies may be frequent in longitudinal studies (Romeo, 1997). As in other studies, several common discrepancies were noted in my study as well. For example, in several instances, participants reported no NSAID use at Wave 1; however, at Wave 2 these participants reported NSAID use that predated Wave 1. Due to the likelihood of recall bias, the information that was given at the time of the medication inventory was considered to be the most reliable (in this case; no NSAID use at Wave 1). Similar situations were dealt with in the same manner. If there were discrepancies between the information gathered at the time of the medication inventory and the information that was obtained by recall, the information gathered at the medication inventory was considered the most reliable and was used in this study.

In some instances, inconsistencies in reporting resulted in another problem dating the onset of NSAID use. If the actual date for which initiation of NSAIDs was unknown, such as in the case given above (no reported NSAID use at Wave 1 but reported NSAID use at Wave 2 that predated Wave 1) then the midpoint between the interval between Waves 1 and 2 was adopted as the start date, which was subsequently converted into the age of use. For example, if a participant was age 76 at Wave 2, and reported NSAID use at Wave 1 but his/her records show that at Wave 1 he/she reported no NSAID use during this time then the midpoint between Wave 1 and 2 was taken (1.5) and deducted from his/her Wave 2 age (76) as the age of actual age of the initiation of NSAID use. Therefore, in this case, the actual initiation of NSAID use was estimated to be 74.5 years

of age ( $76 - 1.5 = 74.5$ ). This approach has been used previously in longitudinal research methodology when there is conflicting information, or on studies of recanting behavior, and is considered an unbiased estimate for capturing inconsistent longitudinal data (Fendrich & Rosenbaum, 2003; Romeo, 1997). For all discrepancies of reported NSAID use between study waves, I adopted the midpoint between study waves as the time of NSAID onset. In the case where there was reported NSAID use at Wave 1, but the participant did not know the beginning of the NSAID use, I calculated the weighted average of all the time intervals between study waves (Waves 1 through 4) and divided by two (1.8 years, or 21.68 months).

### **Statistical Analyses**

For research questions examining the relationship of NSAID use to cognitive or functional decline, I used linear mixed effects models in statistical analyses. The data gathered in this study are longitudinal in nature, resulting in several time points of data that are correlated. Traditional generalized linear models are not appropriate for examining such data because they assume that all observation points are independent of each other (Singer & Willett, 2003). An advantage of linear mixed models is that they accommodate observations that are dependent or correlated (Singer & Willett, 2003). In addition, linear mixed effects models allow the examination of both random and fixed effects, whereas traditional generalized linear models only allow the examination of fixed effects (Singer & Willett, 2003). Fixed and random effects can best be explained in that fixed effects refer to a certain option from a fixed set of options whereas random effects refer to a certain option from an infinite array of options (Singer & Willett, 2003). In the

present analyses, I included both fixed effects (e.g., NSAID use, covariates such as gender) as well as random effects (e.g., time). In this case, time was treated as both a fixed effect (to obtain effect estimates) and a random effect because the follow-up time of each participant varied widely.

To address research question one, whether NSAID use affects AD progression, a series of mixed effects models were conducted for two forms of dementia outcome; MMSE and CDR-SB scores. In these models, ever/never NSAID use was the independent variable (fixed effect of NSAID use, with time treated as both fixed and random). MMSE and CDR-SB scores were the dependent variables. To address research question two, whether the timing of NSAID use had an effect on AD progression, a series of mixed effects models were conducted, where the initiation of NSAID use before dementia onset, after dementia onset, or both was the independent variable and MMSE and CDR-SB scores were the dependent variables. Again NSAID use was treated as a fixed effect, and time as both fixed and random effects. To address research question three, whether the duration of NSAID use affects AD progression, a series of mixed effects models were fit with MMSE and CDR-SB scores serving as the dependent variables. Duration of NSAID use was operationalized as years of continuous use and served as the independent variable (fixed effect). Time was treated as both a fixed and random effect. For each of these analyses I also tested the effects of the following covariates: gender, dementia duration, age, and education. Based on the research conducted by Breitner and Zandi (2001), regarding age and NSAID use interaction, I also interacted NSAID use, as defined by research questions 1-3, with participant age at AD onset to test for possible interactive effects between these two variables.

In addition, in order to maximize the effect of timing and duration of NSAID use, I conducted the above analyses with two groups: (a) at least 2 years of preonset NSAID use *and* at least some postonset NSAID use, and (b) no NSAID use. In these models, NSAID use versus no use was the independent variable (fixed effect of NSAID use, with time treated as both fixed and random) and MMSE and CDR-SB scores were the dependent variables.

For research question four, to examine whether the presence of APOE  $\epsilon 4$  modifies the effects of NSAID use on AD progression, I tested the interaction between NSAID use and the presence or absence of APOE and its effects on AD progression using linear mixed effects models. In this research question, NSAID use was defined as either ever/never NSAID use, NSAID use before, after, or both before and after AD onset, and as years of continuous use.

To examine an association between NSAID use and survival duration (or mortality), I used survival analyses. Survival analysis examines whether the variation of an occurrence of an event (hazard) systematically varies with a given set of predictors (Singer & Willett, 2003). Basically, the variable of interest in a survival model is the amount of time that passes until an event occurs (Singer & Willett, 2003). The time variable can be expressed in years, months, and so forth, or even the age of an individual until an event occurs. The event can be expressed as any designated experience of interest such as death, onset of an illness or disease, end of a treatment program, and so forth. Cox regression models (also called *proportional hazards modeling*) are a type of survival analyses and are currently the most commonly methods used in the survival analyses family (Singer & Willett, 2003). One of the reasons for its popularity is because

it allows the use of time-dependent covariates that may change in value over the course of the observation period (Cox & Oakes, 1984). In this project, NSAID use changed often over the course of the study, and therefore Cox regression models were used in analyses to answer the question of whether NSAID use affected mortality. Mortality served as the event, and time until death served as the dependent variable. NSAID use served as the independent variable. Hazard risk ratios (HR) were calculated to assess the relative risk of each of the above individual variables on the mortality of participants in the study. An HR of one can be interpreted as there is no risk difference between groups, whereas an HR greater than one indicates a greater chance of an event in the exposed group than in the unexposed group. An HR of less than one indicates a less likely chance of an event in the exposed group than the unexposed group. An HR either greater than or less than one can be subtracted from 1; the remainder (absolute value) represents the chance of an occurrence of the event in the exposed group relative to the unexposed group. For example, a HR of 1.45 can be interpreted as  $1 - 1.45$ , or .45, or a 45% increase in risk of an event in the exposed group as compared with the unexposed group. A HR of .23 can be interpreted as  $1 - .23$ , or .77, or a 77% decrease in risk in the exposed group compared to the control group.

## CHAPTER IV

## RESULTS

In this sample, there are significantly more female than male participants (approximately 66%,  $p < .01$ ) of the total 328 participants. The average age of the study participants at study baseline was approximately 84 years ( $SD = 6.45$ ). Participants had an average of approximately 3 visits (3.13) following dementia diagnosis ( $SD = 2.47$ ), and an average of 13.2 years of education ( $SD = 3.00$ ). Both baseline MMSE and CDR-SB have ranges of one to thirty, with MMSE scores averaging 21.92 points ( $SD = 4.6$ ) and CDR-SB scores averaging 6.01 points ( $SD = 3.38$ ). As mentioned previously, a score of 21.92 points on the MMSE is interpreted as mild dementia, whereas a score of 6.01 on the CDR-SB is interpreted as mild functional impairment. The sample characteristics are summarized in Table 1.

As can be seen from Table 1, study participants did not each receive the same amount of follow-up visits. The range of potential visits was 1-10, with the mean amount of visits being 3.13 ( $SD = 2.47$ ). The reasons for participants not receiving a follow-up were due to incomplete visits, subject refusal, participant deceased, moved or were temporarily out of the area, or could not be located. Any other circumstances for which participants did not complete the visits were coded as “other.” The primary reason for loss to follow-up or drop out was mortality as illustrated in Figure 2 below.

There were 297 out of 328 participants who completed the MMSE at their baseline visit. For those who did complete the MMSE, the majority were female (67% to 33%), had approximately 13.4 years of education, were approximately 84 years old, and



Table 1

*Summary of Participant Characteristics at Baseline*

Sample characteristics	Number	%	Mean	SD
Gender				
Male	112	34.1**		
Female	216	65.9**		
APOE ε4 type				
One allele	128	39.0		
Two alleles	19	5.8		
Place of residence				
Home	265	80.8		
Nursing facility unlocked	41	12.5		
Skilled nursing facility	22	6.7		
Education	328		13.20	3.00
Age at baseline	328		84.21	6.45
Dementia duration	328		1.71	1.26
Follow-up visits	327		3.13	2.47
Baseline MMSE	297		21.92	4.60
Baseline CDR	327		6.01	3.38

\*\* $p < .01$ .

at baseline, had been identified with dementia for approximately 1.71 years prior to baseline measures. There were no significant differences in gender for those who did and did not complete the MMSE at baseline, neither did participants who did not complete the MMSE at baseline differ in educational attainment,  $T = 1.77$ ,  $df = 326$ ,  $p = .078$ , or dementia duration at baseline,  $T = .014$ ,  $df = 326$ ,  $p = .99$ , from those that did complete the MMSE at baseline. However, participants who completed baseline MMSE scores were younger at dementia onset than participants who did not complete baseline MMSE

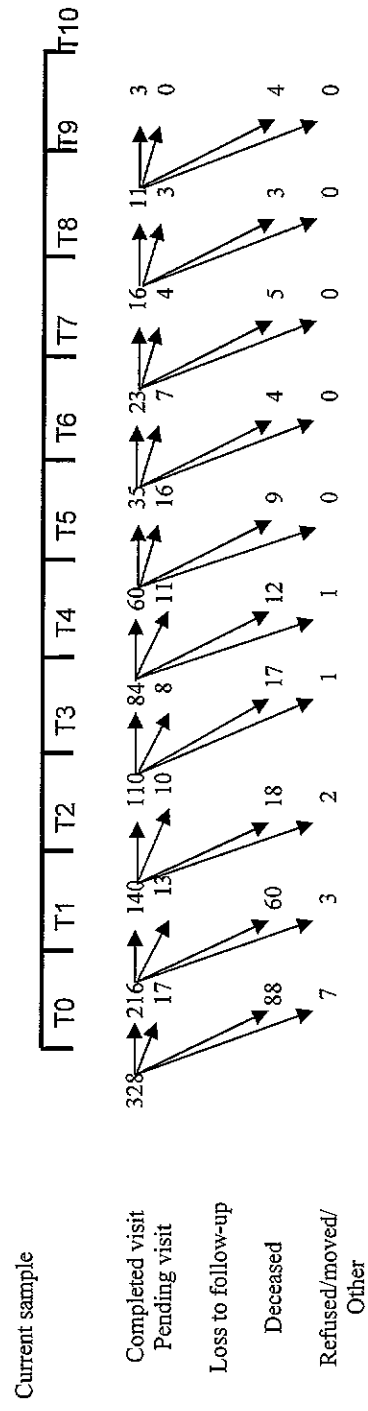


Figure 2. Follow-up characteristics of current sample.

scores,  $T = -2.74$ ,  $df = 326$ ,  $p = .007$ . Participants who did not complete baseline MMSE scores were indicative of not completing the MMSE in other study visits. Only 3 of the 31 participants who did not complete the MMSE at baseline had three or more consistent MMSE scores at follow-up visits. Table 2 provides information regarding those who did and did not complete the MMSE.

### Cognitive Trajectory—MMSE

Those who completed the MMSE averaged approximately 21.92 points ( $SD = 4.60$ ). The distribution of scores followed a normal curve for baseline scores, but deviated from normality with an increasing number of visits (number of completed MMSEs decreased). As the number of visits decreased, along with the number of completed MMSE scores, distributions began to appear more bimodal in nature.

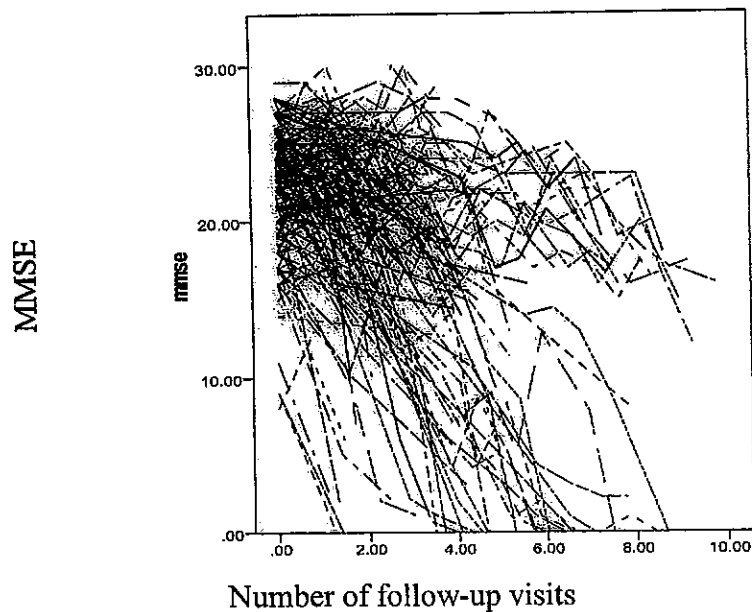
The mean MMSE scores decreased consistently throughout each visit, falling on average .67 points between each visit ( $SD = 1.33$ ). However, there was much variability in individual trajectories on the MMSE between each visit. To illustrate this, a trajectory Plot of individual scores on the MMSE is presented in Figure 3.

Table 2

#### *Descriptive Information of MMSE Completers and Noncompleters*

Sample characteristics	Complete MMSE				Did not complete MMSE			
	Number	%	Mean	<i>SD</i>	Number	%	Mean	<i>SD</i>
Gender								
Male	98	33.0**			14	45.2		
Female	199	67.0**			17	54.8		
Education	297		13.39	2.96	31		12.39	3.33
Age at dementia onset	297		83.90	6.36	31		87.19	6.6
Dementia duration at baseline	297		1.71	1.27	31		1.71	1.43

\*\*  $p < .01$ .



*Figure 3.* Trajectory of MMSE scores by visit.

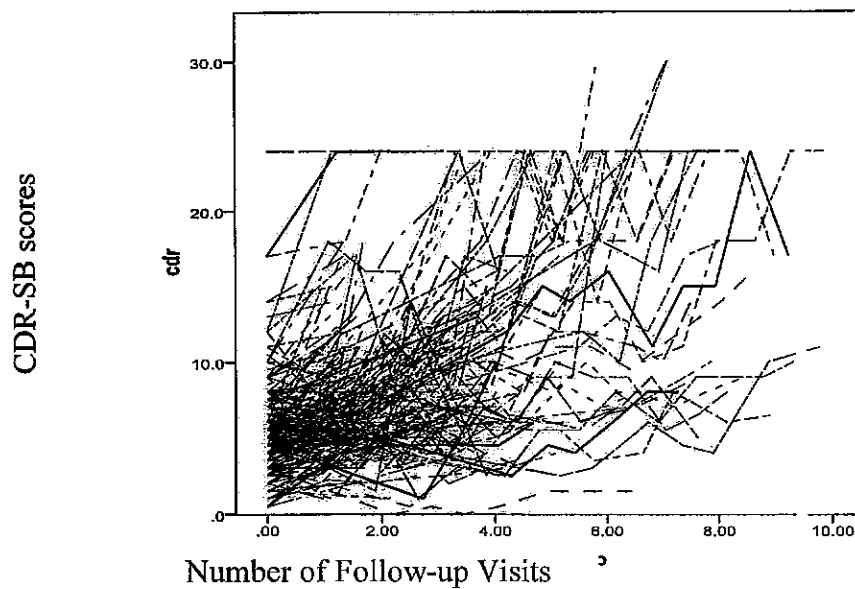
### **Functional Trajectory--CDR-SB**

Nearly all participants had CDR-SB scores at baseline, with only one participant lacking a score. Mean CDR-SB scores at baseline were 5.98 ( $SD = 3.38$ ). The distribution of CDR-SB scores at baseline was approximately normal in shape. However, similar to the MMSE scores, deviated from normality as visit number increased.

The mean CDR-SB scores increased consistently throughout each visit, increasing on average .6 points between each visit ( $SD = 2.35$ ). However, there was much variability in individual trajectories on the MMSE between each visit. To illustrate this, a trajectory plot of individual scores on the MMSE is presented in Figure 4.

### **Survival Duration and Mortality**

As mentioned, participant mortality was determined by newspaper obituaries



*Figure 4.* Trajectory of CDR-SB scores by visit.

and by quarterly reports from the state of Utah Department of Vital Statistics. From these records, 68% ( $n = 223$ ) of the 328 participants had passed away by the date of the dataset creation (November 6, 2007). There were significantly more females than males in both the deceased and nondeceased groups, but there were no differences between the two groups in terms of dementia duration or level of education. Subjects who were deceased as of November 6, 2007, were significantly older at age of dementia onset than individuals not-deceased as of this date. Descriptive information about the deceased and nondeceased groups can be found in Table 3.

### **Outline of Results**

The research questions posed before the Results section indicated two different types of questions were being asked: (a) regarding the trend of decline in cognitive and functional ability of the participants in this study, and (b) regarding the rate of mortality

Table 3

*Descriptive Information on Participant Mortality*

Sample characteristics	Nondeceased				Deceased			
	Number	%	Mean	SD	Number	%	Mean	SD
Gender								
Male	34	32.4**			78	35.0**		
Female	71	67.6**			145	65.0**		
Time in study (in years)	105		4.38	2.98	222		4.43	2.53
Education	105		13.30	2.98	223		13.15	3.02
Age at dementia onset	105		81.42*	5.89	223		85.42*	6.35
Dementia duration at baseline	105		1.54	1.17	223		1.80	1.29

\* significant at the 0.001 level.

\*\* significant &lt; 0.0001 level.

of participants in this study. Although the statistical analyses used to answer these questions were different in nature, the results from each analysis will be presented in reference to each research question. For example, for research question 1, both the results from the linear mixed models and the Cox regression models will be presented in order to respond to this research question. Following research questions will be answered in a similar fashion.

**Research Question 1: Does any NSAID use taken during  
the course of dementia affect the rate of cognitive  
and functional decline and survival duration  
of individuals with AD?**

**Cognitive and Functional Decline—  
Linear mixed models**

According to the criteria of ever being exposed to NSAIDs, approximately 56% (56.4%,  $N = 185$ ) of the individuals in this study had used NSAIDs at some point in their

lives. There were significantly more females than males who used NSAIDs,  $\chi^2= 32.05$ ,  $df=1$ ,  $p < 0.001$ , and also more females than males in those who did not use NSAIDs,  $\chi^2= 43.54$ ,  $df = 1$ ,  $p < 0.001$ ), but there were no differences in age at baseline or education level between users and nonusers,  $T = 0.364$ ,  $df = 326$ ,  $p = 0.716$ ;  $T = 0.374$ ,  $df = 326$ ,  $p = 0.709$ . There were also no differences on baseline MMSE and CDR-SB scores between NSAID users versus nonusers,  $T = -0.066$ ,  $df = 295$ ,  $p = 0.947$ ;  $T = 1.174$ ,  $df = 325$ ,  $p = 0.241$ . Descriptive information on NSAID users and nonusers are displayed in Table 4.

I also examined whether NSAID versus non-NSAID users differed in frequency of medical comorbidities histories up until study baseline. Among these were (in order as listed in Table 5): any history of the following; respiratory distress (asthma, frequent bouts of pneumonia, emphysema, chronic bronchitis); cardiovascular accident (CVA) or transient ischemic attack (TIA); myocardial infarction (MI); angioplasty; chronic pain or inflammation (stemming from chronic headaches, chronic pain conditions, past operations); hypertension; high cholesterol levels; diabetes; head injury (HI); cancer; and angina. There were relatively few differences between NSAID users and nonusers on the variety of these different medical comorbidities. Among all those listed, only hypertension,  $\chi^2= 7.15$ ,  $df=1$ ,  $p < 0.01$ , and chronic pain,  $\chi^2= 8.56$ ,  $df=1$ ,  $p < 0.01$ , significantly distinguished the two groups, with having a history of chronic pain and hypertension problems more likely in the NSAID than in the non-NSAID group.

Table 5 lists the frequencies and proportions between these two groups in terms of the medical comorbidities discussed.

Table 4

*Descriptive Information for NSAID Users and Nonusers*

Sample characteristics	No-NSAID use				NSAID use			
	Number	%	Mean	SD	Number	%	Mean	SD
Gender								
Male	58	40.6**			54	29.2**		
Female	85	59.1**			131	70.8**		
Age at dementia onset	143		84.36	6.46	185		84.10	6.45
Education	143		13.27	3.17	185		13.14	2.88
Baseline MMSE	129		21.90	4.12	168		21.94	4.95
Baseline CDR	143		6.23	3.45	184		5.79	3.33

Table 5

*Medical Comorbidities Between NSAID Users and Nonusers*

		No NSAID use		NSAID use	
		NO	YES	NO	YES
Any respiratory	<i>N</i>	116	28	151	33
	(%)	(80.6)	(19.4)	(82.1)	(17.9)
Any CVA/TIA		107	37	134	50
		(74.3)	(25.7)	(72.8)	(27.2)
Any MI		124	20	153	31
		(86.1)	(13.9)	(83.2)	(16.8)
Any CBG surgery		133	11	175	9
		(92.4)	(7.6)	(95.1)	(4.9)
Any angioplasty		136	8	174	10
		(94.4)	(5.6)	(94.6)	(5.4)
Any pain**		101	43	101	83
		(70.1)	(29.9)	(54.9)	(45.1)
Any hypertension**		67	77	58	126
		(46.5)	(53.5)	(31.5)	(68.5)
Any cholesterol		96	48	109	75
		(66.7)	(33.3)	(59.2)	(40.8)
Any diabetes		115	29	149	35
		(79.9)	(20.1)	(81.0)	(19.0)
Any HI		96	48	123	61
		(66.7)	(33.3)	(66.8)	(33.2)
Any cancer		142	2	179	5
		(98.2)	(1.4)	(97.3)	(2.7)
Any angina		139	5	179	5
		(96.5)	(3.5)	(97.3)	(2.7)

\*\*Significant differences between NSAIDs and non-NSAID users at the .01 level.



### MMSE Scores

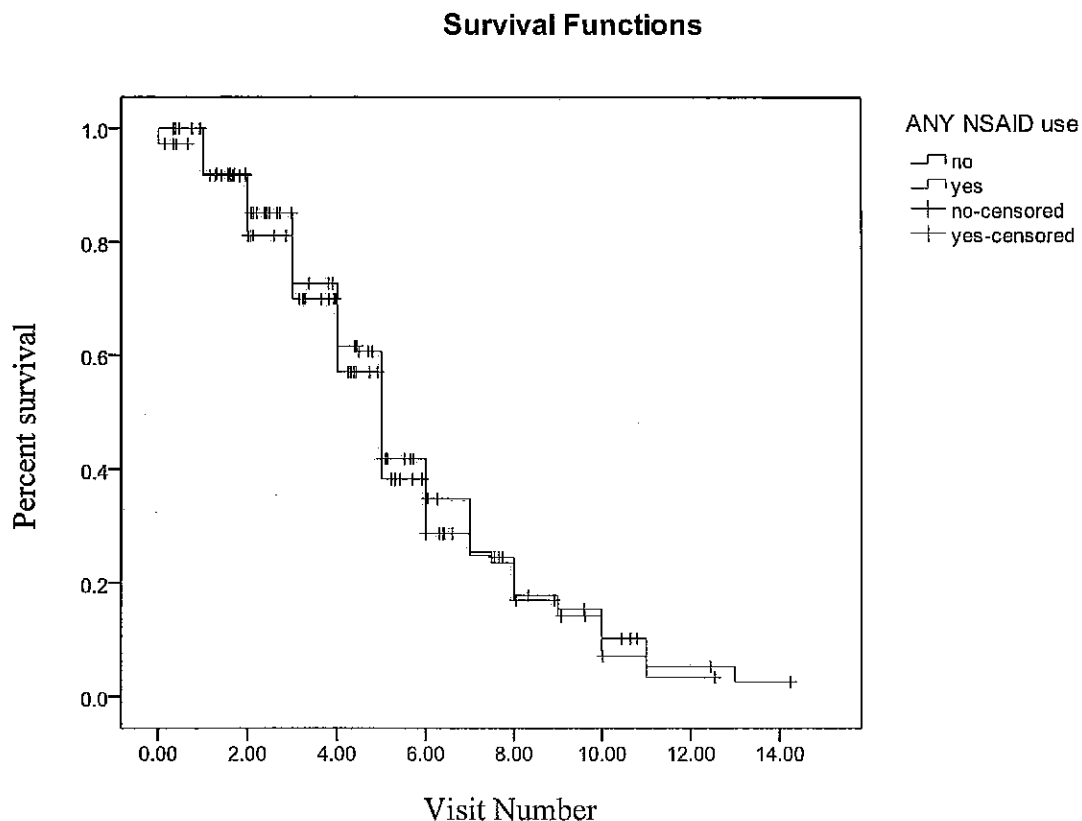
Linear mixed models demonstrated that MMSE scores significantly decreased over time,  $n = 328$ ,  $T = -13.06$ ,  $p < 0.001$ . Ever/never use of an NSAID medication was not significantly related with subject's average MMSE scores,  $LR\chi^2 = .051$ ,  $df = 2$ ,  $p = 0.956$ , nor the rate of cognitive decline,  $LR\chi^2 = 1.67$ ,  $df = 4$ ,  $p = 0.79$ . To examine whether there may be any effect of NSAIDs among those with mild dementia, I also analyzed data restricted to only participants whose CDR-SB score was less than or equal to 1 at the initial baseline visit. There was no effect of NSAID use on overall MMSE scores,  $LR\chi^2 = 1.48$ ,  $df = 2$ ,  $p = 0.47$ , or rate of decline over time,  $LR\chi^2 = 1.86$ ,  $df = 4$ ,  $p = 0.60$ . The following covariates were added to the model: level of education, age at dementia onset, dementia duration, gender, and APOE gene presence/absence. The results showed that greater levels of education were associated with overall higher MMSE scores,  $LR\chi^2 = 6.57$ ,  $df = 1$ ,  $p < 0.01$ ,  $\beta = 0.23$ , and for those with longer dementia duration before diagnosis had lower overall MMSE scores,  $LR\chi^2 = 27.83$ ,  $df = 1$ ,  $p < 0.001$ ,  $\beta = -1.07$ . Females declined faster than males on MMSE scores,  $LR\chi^2 = 6.50$ ,  $df = 1$ ,  $p = 0.01$ ,  $\beta = -.69$ . There were no significant interactions between age of AD onset and NSAID use. In the presence of the covariates, the null findings for NSAID use on MMSE scores remained,  $LR\chi^2 = 2.86$ ,  $df = 2$ ,  $p = 0.29$ , as with rate of cognitive decline,  $LR\chi^2 = 4.10$ ,  $df = 4$ ,  $p = 0.35$ .

### CDR-SB Scores

Linear Mixed Models demonstrated that CDR-SB scores significantly increased over time,  $n = 328$ ,  $T = 12.96$ ,  $p < 0.001$ . However, linear mixed models demonstrated

that ever/never NSAID use did not significantly affect overall CDR-SB scores,  $LR\chi^2 = 0.30$ ,  $df = 2$ ,  $p = 0.86$ , nor the rate of change over time,  $LR\chi^2 = 3.276$ ,  $df = 4$ ,  $p = 0.51$ . There was also no effect of NSAID use among the subgroup of persons starting out with mild dementia on overall CDR-SB overall scores,  $CDR-SBs \leq 1$ ;  $n = 283$ ,  $LR\chi^2 = 1.23$ ,  $df = 2$ ,  $p = 0.54$ , nor rate of CDR-SB change over time,  $LR\chi^2 = 2.33$ ,  $df = 2$ ,  $p = 0.32$ . When adding covariates of education, age at dementia onset, dementia duration, gender, and APOE genotype, individuals with a longer dementia duration had higher initial CDR-SB scores (greater impairment) than individuals with shorter dementia duration,  $LR\chi^2 = 63.73$ ,  $df = 1$ ,  $p < 0.001$ ,  $\beta = 1.09$ . There was also a trend for males having significantly greater overall CDR-SB scores (greater impairment) than females,  $LR\chi^2 = 3.642$ ,  $df = 1$ ,  $p = 0.055$ ,  $\beta = 0.70$ . Age interactions with NSAID use showed no significant differences in overall CDR-SB scores,  $LR\chi^2 = 2.87$ ,  $df = 2$ ,  $p = 0.23$ , nor rates of CDR-SB increase throughout study visits,  $LR\chi^2 = 1.42$ ,  $df = 4$ ,  $p = 0.84$ .

**Cox Regression (Mortality).** To examine the relationship between any NSAID use and mortality, I plotted mortality and its relationship to timing of visit using a Kaplan-Meier plot. As displayed in Figure 5, there is very little separation between survival curves for those with versus without NSAID use. Additionally, the estimated median between the two groups (NSAID use vs. no NSAID use) on length of survival time did not appear to contain any significant differences (median of NSAID group = 5.522 [standard error = .282], median of no NSAID group = 5.502 [standard error = .289]). A log rank test showed no significant relationship between the survival times of subjects with NSAID and no NSAID use,  $\chi^2 = 0.013$ ,  $df = 1$ ,  $p = 0.91$ .



*Figure 5.* Kaplan Meier plot of ever/never NSAID use.

The results of the Cox Regression model were similar to linear mixed model results. Any NSAID use, regardless of length of use or timing of use, was not significantly associated with mortality (Hazard Ratio [HR] = 1.023,  $df = 1$ ,  $p = 0.867$ , CI = .78, 1.34). When including the covariates education, age at baseline, gender and APOE genotype, earlier onset age of dementia was associated with shorter survival duration (HR = 1.09,  $df = 1$ ,  $p < 0.001$ , CI = 1.07, 1.12), as did male gender (HR = 1.436,  $df = 1$ ,  $p = .01$ , CI = 1.08, 1.91).

**Research Question 2: Does the initiation of NSAID use, before  
or after dementia diagnosis, affect the rate of cognitive  
and functional decline and survival duration in  
individuals with AD?**

For NSAID use before, after, and both before and after AD diagnosis I created a variable reflecting four mutually exclusive groups: (a) subjects who had never taken NSAIDs, (b) subjects who had NSAID use *only* prior to AD diagnosis, (c) subjects who had NSAID use *only* following AD diagnosis, and (d) individuals who had NSAID use *both* pre- and post-AD diagnosis. When dividing NSAID use into these four separate categories, 44% (43.6%,  $n = 143$ ) had never used NSAIDs at any point in their lives. Fifty-seven individuals (17.4%) used NSAIDs prior to their AD onset only, while 32 individuals (9.8%) used NSAID medications following AD onset only. Ninety-six individuals (29.2%) had used NSAIDs both prior to and after AD onset. There were significantly more females than males in three of the four levels of NSAID exposure: (a) no NSAID use ever,  $n = 143$ ,  $\chi^2 = 5.44$ ,  $p = 0.02$ , (b) NSAID use before AD onset only,  $n = 57$ ,  $\chi^2 = 7.737$ ,  $p = 0.005$ , and (c) NSAID use both pre- and post-AD onset,  $n = 96$ ,  $\chi^2 = 27.38$ ,  $p < 0.00$ . There were no significant differences in proportion of males and females in the third group, NSAID use following AD onset,  $n = 32$ ,  $\chi^2 = .5$ ,  $p = 0.48$ .

One-way analysis of variance (ANOVA) demonstrated that NSAID group did not differ in terms of baseline MMSE and CDR-SB scores,  $F = 0.15$ ,  $df = 293$ ,  $p = 0.93$ ;  $F = 0.75$ ,  $df = 325$ ,  $p = 0.52$ ; age,  $F = 1.48$ ,  $df = 327$ ,  $p = 0.22$ ; and education,  $F = 0.24$ ,

$df = 327, p = .871$ . Characteristics of NSAID exposure level according to these four levels are illustrated in Table 6.

### **MMSE Scores**

Linear mixed models demonstrated that the timing of NSAID use exposure, before, after, or both before and after AD diagnosis, was not significantly associated with overall MMSE scores,  $LR \chi^2 = .44, df = 4, p = 0.97$ . Also, the timing of NSAID exposure did not significantly impact the rate of cognitive decline,  $LR \chi^2 = 3.30, df = 6, p = 0.51$ . There was no effect of NSAID use on overall MMSE scores among the subgroup of persons starting out with mild dementia (global CDR-SBs  $\leq 1; n = 283$ ,  $LR \chi^2 = 6.2, df = 4, p = 0.18$ ), nor rate of cognitive decline,  $LR \chi^2 = 8.7, df = 6, p = 0.19$ . Inclusion of covariates level of education, age at dementia onset, dementia duration, gender, and APOE genotype did not alter the relationship between NSAID use and overall MMSE scores or decline in MMSE over time. Subjects with higher levels of education demonstrated higher overall MMSE scores than subjects with lower levels of education.  $LR \chi^2 = 5.21, df = 1, p = 0.02, \beta = 0.2$ . The final model also showed that subjects who had longer dementia duration periods had lower overall MMSE scores,  $LR \chi^2 = 28.51, df = 1, p < 0.001, \beta = -1.09$ . The final model showed that female subjects also declined quicker on the MMSE than males,  $LR \chi^2 = 6.45, df = 1, p = 0.01, \beta = -0.88$ . Age interactions with NSAID use showed no significant differences in overall MMSE scores,  $LR \chi^2 = 2.67, df = 1, p = 0.11$ , nor rates of MMSE decrease throughout study visits.  $LR \chi^2 = 3.01, df = 3, p = 0.39$ .

Table 6

#### Four-level NSAID Variable Descriptives

Sample characteristics	Non-NSAID users			Pre-AD NSAID use only			Post-AD NSAID use only			Both pre- and post-AD NSAID use		
	Number	%	Mean SD	Number	%	Mean SD	Number	%	Mean SD	Number	%	Mean SD
Gender												
Male	58	40.6**		18	31.6**		14	43.8		22	23.2**	
Female	85	59.1**		39	68.4**		18	56.3		73	76.8**	
Age at dementia onset	143		84.36 6.46	57		85.37 5.46	32		82.41 7.15	95		84.05 6.54
Education	143		13.27 3.17	57		13.33 3.10	32		13.28 2.58	95		12.98 2.87
Baseline MMSE	129		21.90 4.12	53		22.25 4.68	29		21.85 3.65	85		21.71 5.50
Baseline CDR	143		6.23 3.45	57		5.45 2.55	32		6.13 1.97	94		5.90 4.07

\*\* = significant at the .01 level.

### CDR-SB Scores

NSAID use, before or after AD diagnosis, did not significantly affect overall CDR-SB scores,  $LR\chi^2 = .50$ ,  $df = 4$ ,  $p = 0.96$ , nor rate of change in CDR-SB over time,  $LR\chi^2 = 4.26$ ,  $df = 6$ ,  $p = 0.64$ . There was no effect of NSAID use on overall MMSE scores among the subgroup of persons starting out with mild dementia (global CDR-SB's  $\leq 1$ ;  $n = 283$ ,  $LR\chi^2 = 5.7$ ,  $df = 4$ ,  $p = 0.22$ , nor rate of cognitive decline,  $LR\chi^2 = 5.9$ ,  $df = 6$ ,  $p = 0.43$ . Inclusion of the covariates level of education, age at dementia onset, dementia duration, gender, and APOE genotype did not significantly change the results of the effects of NSAIDs. Subjects with longer periods of dementia duration were associated with higher levels of functional impairment,  $LR\chi^2 = 64.52$ ,  $df = 1$ ,  $p < 0.001$ ,  $\beta = 1.16$ . In addition, males had significantly higher overall CDR-SB scores than women,  $LR\chi^2 = 3.58$ ,  $df = 1$ ,  $p = 0.058$ ,  $\beta = 0.71$ . Age interactions with timing of NSAID use showed no significant differences in overall CDR-SB scores,  $LR\chi^2 = 1.23$ ,  $df = 4$ ,  $p = 0.87$ , nor rates of CDR-SB increase throughout study visits,  $LR\chi^2 = 3.78$ ,  $df = 6$ ,  $p = 0.71$ .

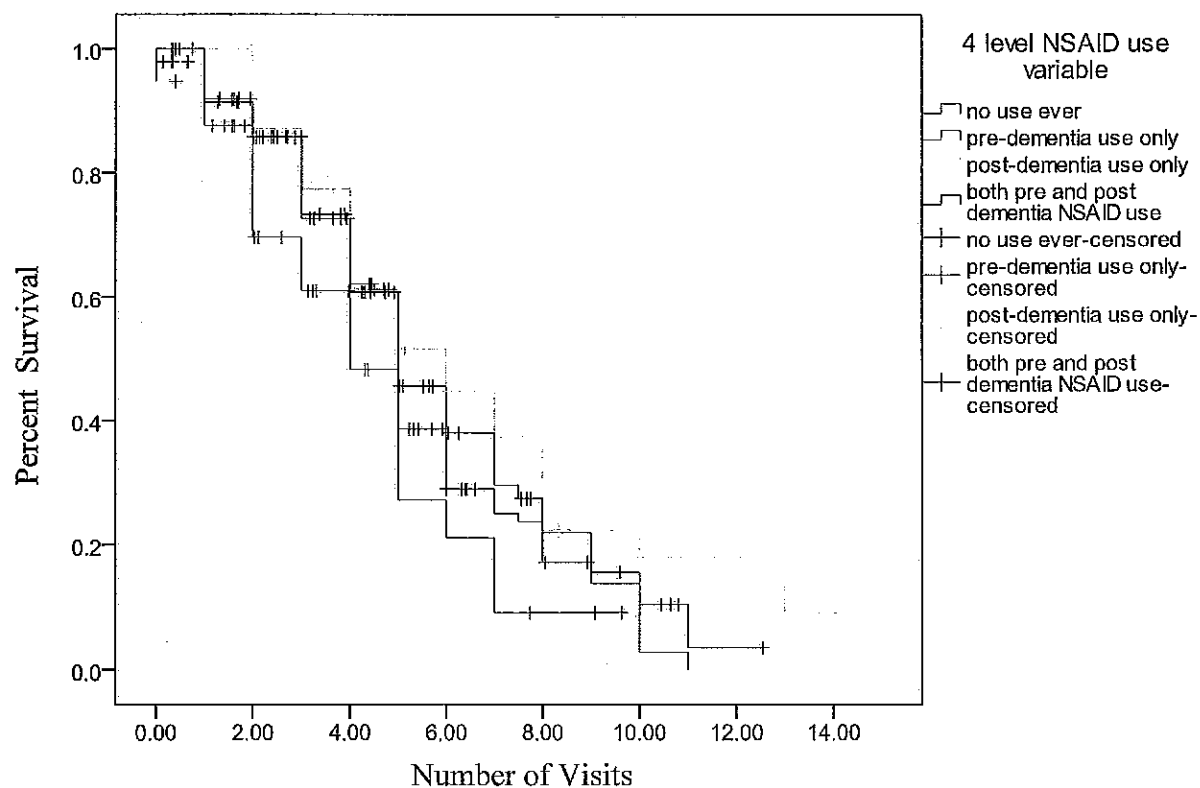
**Cox Regression (mortality).** To examine the relationship between the timing of NSAID use and mortality, I plotted Kaplan-Meier survival curves according to the four levels of NSAID use. As can be seen from the plot below (Figure 6), there appears to be separation of curves between groups 1 and 3. Median survival time also appeared to be different between groups 1 and 3 (no NSAID use versus postdementia NSAID use only). Table 7 displays the median survival times of the four groups.

Despite significant log rank test, timing of NSAID use was not significantly associated with survival duration. However, there appeared to be a trend where members in group 1 (predementia NSAID use only) exhibited a 13% greater risk for death than

Table 7

*Estimated Median Scores for 4 Level NSAID Variable*

	Group 1 (no NSAID use)	Group 2 (Predementia NSAID use only)	Group 3 (Postdementia NSAID use only)	Group 4 (Pre- and postdementia NSAID use)
Estimated medians (SD)	5.50 (.29)	4.30 (.38)	6.90 (.72)	5.59 (.34)



*Figure 6.* Kaplan Meier plot for 4 level NSAID variable.



group 0 (no NSAID use group),  $HR = 1.13$ ,  $df = 3$ ,  $p = 0.07$ ,  $CI = .93, 1.19$ . When including the covariates education, age at baseline, dementia duration, gender and APOE genotype, only onset age for dementia significantly predicted survival outcomes, with older individuals having a 9.3% greater risk of death over younger individuals,  $HR = 1.093$ ,  $df = 1$ ,  $p < 0.001$ ,  $CI = 1.067, 1.119$ .

**Research Question 3: Does the duration of NSAID use affect  
the rate of cognitive and functional decline and  
survival duration in individuals with AD?**

As mentioned above, approximately 56% of the sample had at least some degree of NSAID use. The average duration of NSAID use at any point before, during, or after dementia onset for those with at least one month of use, either pre- or postdementia, or both, was 6.14 years ( $SD = 6.83$ ). Predementia use averaged 4.68 ( $SD = 6.34$ ) years, and postdementia use averaged 1.46 (1.72) months of use. The distribution of NSAID use was positively skewed. Frequency distributions of pre- and postdementia use, as well as total NSAID duration of use are presented below in Figures 7, 8, and 9.

In further exploratory analyses, I expressed duration of NSAID use in tertiles and examined baseline differences in subjects. The first tertile used anywhere from 1 to 30.8 months of NSAID use, the second tertile had anywhere from 30.96 to 70.55 months of NSAID use, and the highest tertile had anywhere from 74 to 569.10 months of NSAID use. One-way ANOVA revealed no significant differences between these three groups in terms of level of education, length of dementia duration, or baseline MMSE or CDR-SB scores,  $F = 0.185$ ,  $df = 2$ ,  $p = 0.86$ ,  $F = 0.672$ ,  $df = 2$ ,  $p = 0.51$ , respectively. However,

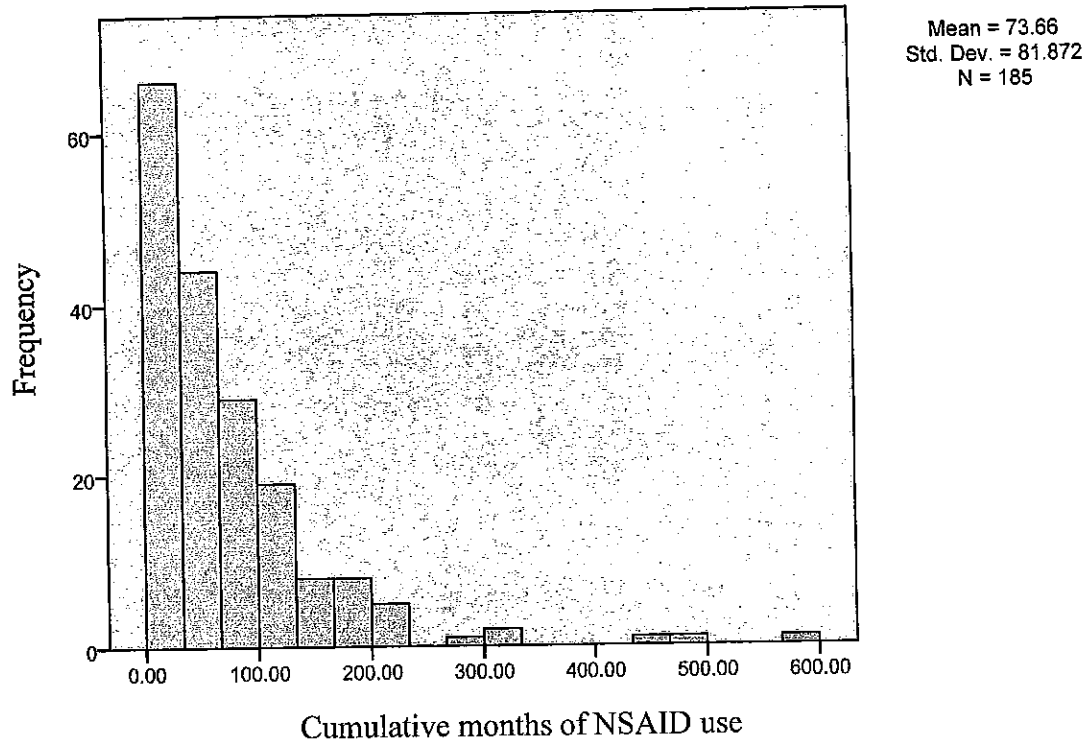


Figure 7. Total NSAID use.

subjects in the first tertile of NSAID use were significantly older than subjects in the last tertile of NSAID use,  $F = 1.63$ ,  $df = 29$ ,  $p = 0.03$ . There was a higher proportion of females than males in each group (Group 1:  $\chi^2 = 4.74$ ,  $df = 1$ ,  $p = 0.03$ ; Group 2:  $\chi^2 = 13.79$ ,  $df = 1$ ,  $p < 0.001$ ; Group 3:  $\chi^2 = 15.25$ ,  $df = 1$ ,  $p < 0.001$ ). Descriptive statistics are provided for each group in Table 8.

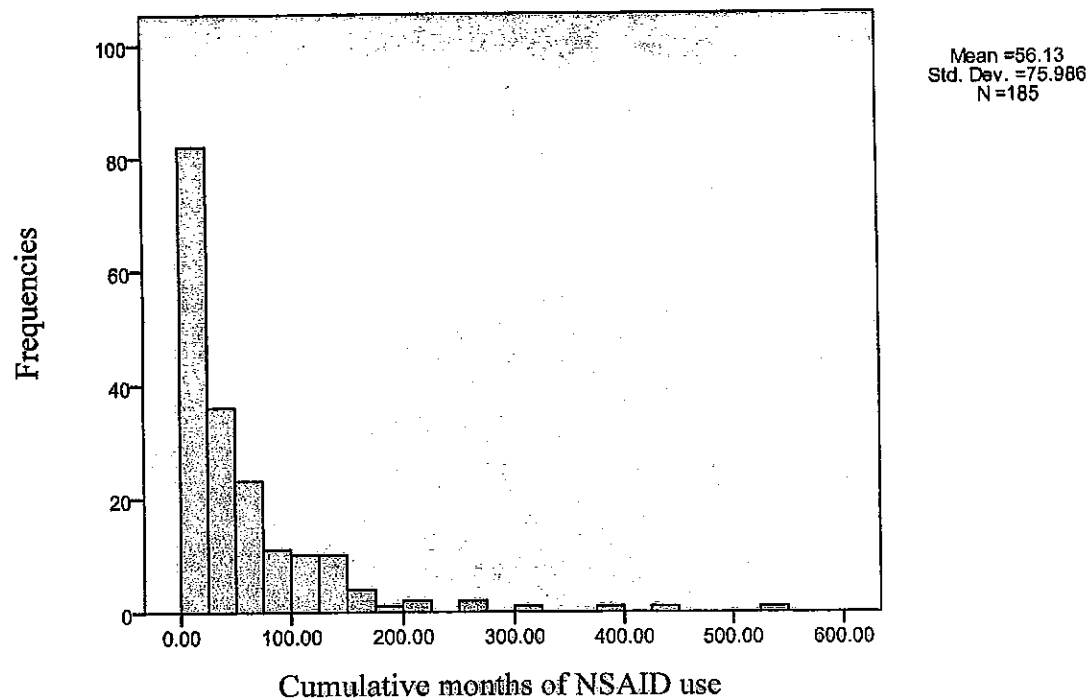
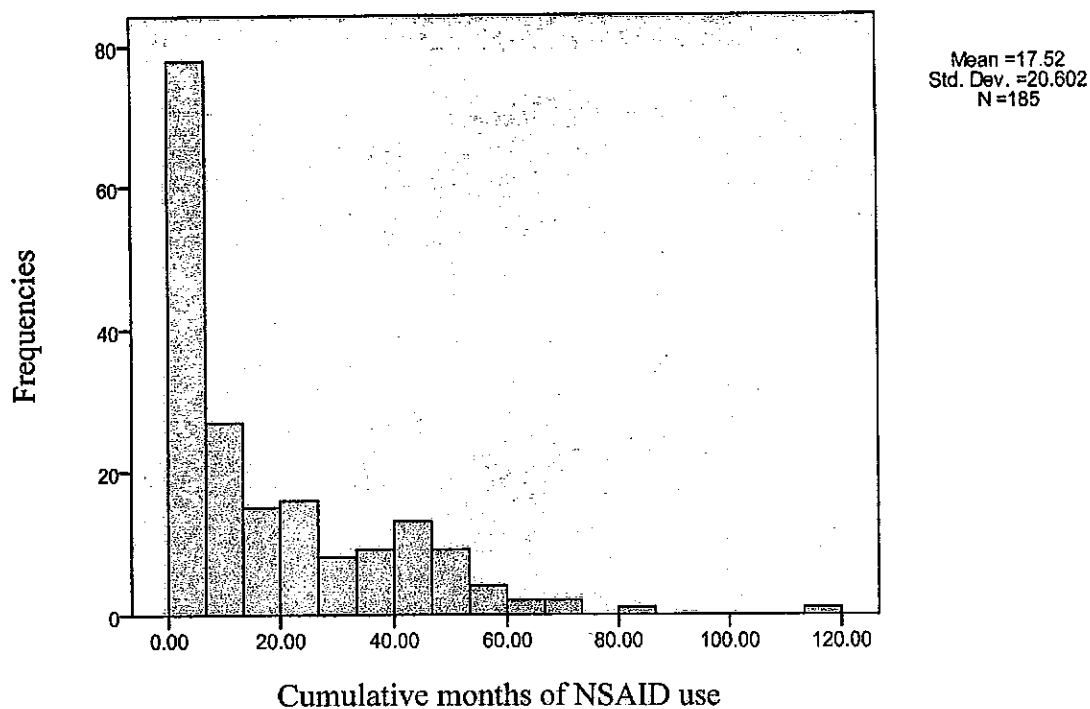


Figure 8. Predementia NSAID use only.

### MMSE Scores

Duration of NSAID use did not significantly affect overall MMSE scores,  $LR\chi^2 = 1.23$ ,  $df = 1$ ,  $p = 0.26$ , nor did duration of NSAID use significantly affect rate of cognitive decline,  $LR\chi^2 = 0.725$ ,  $df = 2$ ,  $p = 0.70$ . There was no effect of NSAID use on overall MMSE scores among the subgroup of persons starting out with mild dementia (global  $CDR-SBs \leq 1$ ;  $n = 283$ ,  $LR\chi^2 = 1.2$ ,  $df = 1$ ,  $p = 0.27$ , nor rate of cognitive decline,  $LR\chi^2 = .89$ ,  $df = 2$ ,  $p = 0.35$ . Addition of the covariates level of education, age at dementia onset, dementia duration, gender, and APOE genotype, did not alter the relationship between NSAID use and MMSE scores. Higher levels of education were associated with



*Figure 9.* Postdementia NSAID use only.

greater overall MMSE scores,  $LR\chi^2 = 5.012$ ,  $\beta = 0.22$ ,  $df = 1$ ,  $p = 0.02$ . Subjects with longer periods of dementia duration at baseline were associated with lower overall MMSE scores,  $LR\chi^2 = 28.057$ ,  $\beta = -1.07$ ,  $df = 1$ ,  $p < 0.001$ . Female subjects were also shown to decline in MMSE scores quicker than males,  $LR\chi^2 = 7.359$ ,  $\beta = 0.78$ ,  $df = 2$ ,  $p = .025$ . To zero in on any NSAID duration effects after dementia onset, I also conducted the same analyses but limited NSAID use duration to NSAID use only following AD onset. However, results from this model were similar to the results in the model above with NSAID use having no effect on overall MMSE scores,  $LR\chi^2 = 1.23$ ,

Table 8

*Descriptives of NSAID Tertile Groups*

Sample Characteristics	Group 1 (first tertile)				Group 2 (second tertile)				Group 3 (third tertile)			
	Number	%	Mean	SD	Number	%	Mean	SD	Number	%	Mean	SD
<b>Gender</b>												
Male	22	36.0*			16	26.2**			16	25.4**		
Female	39	64.0*			45	74.8**			47	74.6**		
Age at dementia onset	61		85.79**	6.04	61		83.97	6.58	63		82.58**	6.40
Education	61		13.68	2.45	61		12.79	3.05	63		12.98	2.72
AD duration	61		1.50	1.21	62		1.73	1.23	62		1.98	1.50
Baseline MMSE	54		22.25	3.83	55		21.82	4.59	59		21.76	6.10
Baseline CDR	61		5.56	2.06	60		5.61	3.03	63		6.18	4.40

\* significant at the .05 level.

\*\* significant at the .001 level.

$df = 1, p = 0.27$ , nor the rate of cognitive decline,  $LR\chi^2 = 4.37, df = 2, p = 0.13$ . Age interactions with duration of NSAID use also showed no significant differences in overall MMSE scores,  $LR\chi^2 = 0.87, df = 1, p = 0.65$ , nor rates of MMSE decline over the study visits,  $LR\chi^2 = 2.53, df = 2, p = 0.28$ .

**CDR-SB Scores**

Duration of NSAID use did not significantly impact overall CDR-SB scores,  $LR\chi^2 = 2.17, df = 1, p = 0.15$ , nor rate of change in CDR-SB scores,  $LR\chi^2 = 3.14, df = 2, p = 0.21$ ). There was no effect of NSAID use on overall MMSE scores among the subgroup of persons starting out with mild dementia,  $LR\chi^2 = .79, df = 1, p = 0.36$ , nor rate of cognitive decline,  $LR\chi^2 = 2.92, df = 2, p = 0.23$ . The addition of the covariates level of education, age at dementia onset, dementia duration, gender, and APOE genotype

did not alter the relationship between duration of NSAID use and CDR-SB. Only dementia duration had any impact on overall CDR-SB scores, showing that longer periods of dementia duration were associated with increased CDR-SB scores,  $LR\chi^2 = 61.75$ ,  $\beta = 1.12$ ,  $df = 1$ ,  $p < 0.001$ . Age interactions with duration of NSAID use also showed no significant differences in overall CDR-SB scores,  $LR\chi^2 = 2.63$ ,  $df = 1$ ,  $p = 0.11$ , nor rates of CDR-SB change over the study visits,  $LR\chi^2 = 1.90$ ,  $df = 2$ ,  $p = 0.17$ .

### **Cox Regression (Mortality)**

Due to the limitations of the data, no Kaplan-Mier plots were able to be produced. However, Cox Regression models were conducted demonstrating that the duration of NSAID use was not significantly associated with risk for mortality,  $HR = 1.04$ ,  $df = 1$ ,  $P = 0.41$ ,  $CI(95) = .996, 1.01$ . Inclusion of the covariates education, age at baseline, gender, and APOE genotype did not alter this result. Earlier onset age of dementia significantly increased one's chances of mortality,  $HR = 1.09$ ,  $df = 1$ ,  $p < 0.001$ ,  $CI = 1.07, 1.12$ , as did male sex,  $HR = 1.427$ ,  $df = 1$ ,  $p = .01$ ,  $CI = 1.08, 1.90$ .

### **Power Analysis**

In view of the null results found in the previous three research questions, I conducted a power analyses to determine whether the current analyses with the linear mixed models were underpowered. According to Fitzmaurice and colleagues (2004), there are several items under consideration when calculating power with longitudinal data: (a) the mean amount of study follow-up visits, (b) the standard deviation of number of follow-up visits, (c) the estimated effect size, and (d) and the number of participants in the study. For the power analyses in this study, I limited the participants to those who

had only completed at least one follow-up visit. Of the 328 participants, only 216 had at least one follow-up visit, therefore restricting my number value in the current analyses to 216 instead of 328 participants. My estimated effect size for the MMSE was 0.27, and for the CDR-SB was 0.54. I selected these values based from findings reported by Mielke et al. (2007) that suggested such effect sizes between antihypertension medications and cognitive and functional decline in a sample of AD patients. In Table 9 are listed the calculated power estimates for effect sizes that range from small (0.2), medium (0.5) and large (0.8), according to Cohen (1988).

As can be seen from the table below, with a chosen effect size of 0.27 for the MMSE and 0.54 for the CDR-SB, the power analysis suggests that this study had adequate power to detect medium and large effect sizes, but not a small effect. Although such results were not discovered in the analyses from this study, such nonsignificant findings are not considered the result of being underpowered.

Table 9

*Power Analyses*

	Estimated power	
	MMSE	CDR
Small effect size (.2)	46%	48%
Medium effect size (.5)	84%	99.5%
Large effect size (.8)	99.9%	99.9%

### **Subgroup Analysis: 2+ Years of Preonset SAID Use**

In analyses examining a subgroup with greatest potential to show an effect for NSAID use (based on the literature), I examined individuals who had at least two years of predementia NSAID use and continued use after dementia onset versus persons who never used NSAIDs. There were 66 individuals who fell into the NSAID use (2+ years of predementia use, and at least some postonset use) group and 262 remaining participants not meeting these criteria. Even with categorizing the data in this manner, results were largely the same as other results attained in this project. Linear mixed models demonstrated that NSAID users (defined as 2+ years of predementia NSAID use) did not differ from nonusers in terms of their overall MMSE scores,  $LR\chi^2 = 2.14$ ,  $df = 2$ ,  $p = 0.35$ , nor rate of cognitive decline,  $LR\chi^2 = 1.04$ ,  $df = 4$ ,  $p = 0.97$ . There were also no overall differences in overall CDR scores between these two groups,  $LR\chi^2 = 3.19$ ,  $df = 2$ ,  $p = .20$ , or CDR change scores through time,  $LR\chi^2 = 3.70$ ,  $df = 4$ ,  $p = 0.45$ . Lastly, there were no differences between these two groups in terms of their risk of mortality,  $HR = 1.11$ ,  $df = 1$ ,  $p = 0.13$ ,  $CI(95) = .09, .17$ .

### **Research Question 4: Is there any evidence of APOE $\epsilon 4$ interaction with NSAID use on the rate of cognitive and functional decline and survival duration among individuals with AD?**

To describe my sample in terms of APOE  $\epsilon 4$  presence, I divided those who possessed at least one APOE  $\epsilon 4$  allele into one group and those that did not into another.



Participants numbering 181 possessed at least one APOE  $\epsilon 4$  allele (55.1%), whereas 147 did not. Table 10 displays the frequency of NSAID use by APOE  $\epsilon 4$  group.

In the APOE  $\epsilon 4$  group 76 participants had no NSAID use and 103 had at least one month of NSAID use. Of the 103 participants in the APOE  $\epsilon 4$  group roughly one third of the group fell into each of the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> tertile use groups. In the no APOE  $\epsilon 4$  group 65 participants had no NSAID use and 82 had at least one month of use. Similarly, as in the APOE  $\epsilon 4$  group, the no APOE  $\epsilon 4$  group had roughly one third of the group in each of the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> tertile use groups. In participants with at least one month of NSAID use, there were no significant differences between the two APOE groups in terms of average total NSAID use,  $T = 0.79$ ,  $df = 180$ ,  $p = 0.43$ .

Table 10

*NSAID Use by APOE  $\epsilon 4$  Group*

	APOE $\epsilon 4$	No APOE $\epsilon 4$
NSAID Use ( $n = 185$ )	103 (56%)	82 (44%)
No NSAID use ( $n = 141$ )	76 (54%)	65 (46%)
Length of use by APOE genotype (Mean/ <i>SD</i> )		
1 <sup>st</sup> tertile (1-30.8 months of NSAID use)	32 (31.1%)	29 (35.4%)
2 <sup>nd</sup> tertile (30.96-70.55 months of NSAID use)	38 (36.9%)	23 (28.0%)
3 <sup>rd</sup> tertile (74.0-569.1 months of NSAID use)	33 (32.0%)	30 (36.6%)
Total months of NSAID use	73.1 (64.82)	83.4 (96.32)

In the results presented above, presence of APOE  $\epsilon 4$  did not significantly affect overall MMSE and CDR-SB scores nor their progression through time. To answer research question 4 (whether effects of NSAID use were modified by genotype at APOE), I tested an interaction between presence of APOE  $\epsilon 4$  and NSAID use as defined in the previous research questions in linear mixed effects models. In reference to ever/never NSAID use, there was no significant interaction between NSAID use and presence of APOE  $\epsilon 4$  in predicting overall MMSE or CDR-SB scores,  $LR\chi^2 = 3.01$ ,  $df = 2$ ,  $p = 0.18$ ,  $LR\chi^2 = 4.06$ ,  $df = 2$ ,  $p = 0.13$ , nor the rate of change in MMSE or CDR-SB scores,  $LR\chi^2 = 4.89$ ,  $df = 3$ ,  $p = 0.30$ ,  $LR\chi^2 = 6.05$ ,  $df = 3$ ,  $p = 0.11$ . In reference to the timing of NSAID use, before or after AD onset, there was no interaction between NSAID use and APOE and their effect on overall MMSE or CDR-SB scores,  $LR\chi^2 = 6.45$ ,  $df = 4$ ,  $p = 0.17$ ,  $LR\chi^2 = 5.87$ ,  $df = 4$ ,  $p = 0.21$ , nor rate of change in MMSE and CDR-SB scores,  $LR\chi^2 = 7.55$ ,  $df = 6$ ,  $p = 0.27$ ,  $LR\chi^2 = 5.71$ ,  $df = 6$ ,  $p = 0.46$ . Lastly, the interaction between duration of NSAID use and APOE also did not significantly affect overall MMSE or CDR-SB scores,  $LR\chi^2 = 2.73$ ,  $df = 1$ ,  $p = 0.11$ ,  $LR\chi^2 = 2.32$ ,  $df = 1$ ,  $p = 0.13$ , nor rate of change in MMSE and CDR-SB scores,  $LR\chi^2 = 1.45$ ,  $df = 2$ ,  $p = 0.48$ ,  $LR\chi^2 = 2.84$ ,  $df = 2$ ,  $p = 0.24$ .

## CHAPTER V

## DISCUSSION

In this project I proposed to research the effects of NSAIDs on the progression of cognitive and functional impairment and survival duration in AD. I did this by examining NSAID use in a variety of different ways, specifically, use of any type of NSAID, timing of NSAID use in relation to the onset of dementia, and the duration of NSAID use.

The results from this project suggested that NSAID use, defined by any of the methods described above, does not affect the rate of cognitive or functional decline in persons after the onset of AD. These results support the null hypothesis (no effect). Power analyses that were conducted suggested that there was sufficient power to detect a moderate effect size (approximately .5), which supports the notion that NSAIDs may not have an effect on cognitive or functional decline after the onset of AD. While the study was sufficiently powered to detect moderate or large effect sizes, the power to detect small effects was only 48%.

A discussion of the results found in this study would not be complete without discussing potential reasons for the lack of impact NSAIDs have on AD progression once AD has been diagnosed, despite relatively robust data that suggests NSAIDs can delay the onset of AD (see Literature Review). As reviewed previously, the prophylactic nature of NSAID use on AD results from the antiinflammatory effect NSAIDs have on the central nervous system. Because neuroinflammation plays a significant role in the development of NFTs and beta-amyloid plaques (Frackowiak et al., 1992; Mackenzie et

al., 1995; Perlmutter et al. 1990), medications that decrease inflammation are likely to affect the degree of NFTs and beta-amyloid plaques that build up over time, thus postponing the accumulation of the biological agents responsible for AD. This is the theoretical basis upon which hypothesis of NSAID use and their purported effect on AD progression is based. However, most of the evidence that NSAIDs postpone or delay the onset of AD has risen primarily from epidemiological evidence, not necessarily from RCTs. RCTs that have looked at the onset of AD and its relationship to NSAID medication have not provided such auspicious results. For example, in 2007 the National Institute on Aging (NIA) sponsored a large placebo-controlled RCT of naproxen and celecoxib (both NSAIDs) and their purported effect on the risk of AD. Although the study terminated prematurely due to discovered cardiovascular risks in taking naproxen and celecoxib, analyses of the data gathered prior to termination found no benefit of either NSAID use, but also suggested that naproxen and celecoxib use may lead to an *increased* risk of developing AD (Lyketsos et al., 2007). Lyketsos and colleagues discussed their findings in conjunction with other research that protective effects stem from epidemiologic studies, but not from clinical trials. Results from epidemiological studies may suggest the presence of confounding variables that complicate the relationship between NSAID use and AD risk (Lyketsos et al., 2007).

In addition, the Adult Changes in Thought (ACT) study conducted by Arvanitakis and colleagues (2008), also found an increased risk of AD with associated NSAID use. One difference in this study when compared to other studies in the field was that Arvanitakis and colleagues were able to not only note NSAID use, but the dose of NSAIDs consumed. They divided their sample of NSAID users into three categories: (a)

heavy, (b) moderate, or (c) light NSAID users. In the light to moderate categories, they found no relationship between NSAID users and nonusers in hazard ratios for developing AD. However, they found an increased risk of developing AD with heavy NSAID users, even after adjusting for potential confounding variables, such as age, sex, and education. Their results suggested that dosage is an important variable, and that representing NSAID use as a simple dichotomy of use/no use may lead to spurious or misleading results (Arvanitakis et al., 2008). Other studies have also found that dosage is an important variable to consider when examining the relationship between NSAID use and AD onset and progression (Broe et al., 2000)

The purported link between NSAID use and the development of AD can be questioned, and may only exist under certain conditions, such as for a certain dosage of NSAIDs or in observational studies where potential confounding variables are not fully considered. One of these factors may be age. Well-known studies such as the Rotterdam study have found a negative association between NSAID use and AD onset in younger samples, but no association in older samples (In't Veld et al., 1998). Perhaps studies that do not report a beneficial effect, such as the ACT study (Arvanitakis et al., 2008), reflects differences in age of use and age of the population being studied. The ACT study and many others in the field have studied NSAID use in late life, in much older participants than that of Rotterdam. It is possible that age may be a moderating factor of the effects of NSAID use on AD risk. The literature would suggest a lower risk of AD with NSAIDs in younger but not older individuals (Bennett & Whitmer, 2009).

Another reason for the negative results of this study may have to do with the nature of NSAIDs and how they operate in decreasing inflammation in the brain.

Although NSAIDs may decrease inflammation and the accumulation of neuropathological markers of AD (i.e., NFTs and beta-amyloid plaques), it may be that such prophylactic effects have run their course after NFTs and beta-amyloid plaques have already set in, thus resulting in limited to no effects of NSAIDs after the diagnosis of AD is made. Although there is evidence that NSAIDs can decrease neuroinflammation, thus postponing or decreasing the accumulation of NFTs and amyloid plaques, there is no evidence that suggests NSAIDs can reverse the damage that has already occurred or reverse the amount of NFTs and amyloid plaques that have already aggregated in the brain of persons with AD (Cole & Frautschy, 2010). AD has a long preclinical period. In fact, recent research has suggested that subtle cognitive changes, primarily age-related memory decline, can occur up to decades before the actual clinical presentation of AD symptoms (Caselli et al., 2009). It is possible that the inflammatory processes thought to contribute to AD may also be occurring well before the actual onset of symptoms. Thus, NSAIDs may exert effects in preclinical stages, but may have no effects after the onset of AD. After disease onset, compounds that reverse the damage exerted by the disease (unlikely), prevent further damage, or promote neurogenesis would likely be of benefit; however, these activities are not likely to be part of the medicinal actions of NSAID medications (Cole & Frautschy, 2010).

As an aside, in posthoc analyses, I did attempt to examine possible effects of NSAIDs on those with mild AD, by restricting analyses of the first three research questions to those with a global CDR of  $\leq 1$ , where plaque and NFT burden would likely be lower than those in the advanced stages of the disease. However, the results were largely the same as other results obtained in this study, that NSAIDs did not

significantly affect cognitive or functional outcomes. Additionally, research into the effects of NSAIDs in Mild Cognitive Impairment (MCI), a prodrome to AD, has also yielded negative results, indicating that NSAIDs are not effective in either slowing the cognitive decline of MCI nor the rate of conversion of MCI to AD (Aisen et al., 2008; Thal et al., 2005). This would suggest that at the point of symptom expression, NSAIDs are not an effective treatment to reduce the cognitive decline nor emergence of AD.

While the results of the current project suggest that NSAIDs are not effective in treating AD, it does not necessarily follow that neuroinflammation does not influence the progression of symptoms in AD. Although there is a link between NSAID use and a reduction of inflammation, there is no direct link between peripheral NSAID use and degree of neuroinflammation within the brain. To directly measure the amount of brain inflammation, measurements of inflammatory markers such as tumor necrosis factor-alpha (TNF- $\alpha$ ), C-reactive protein (CRP), and other cytokines (such as interleukins 2, 6) would need to be assayed, preferably from cerebrospinal fluid. Such biomarkers are direct measures of inflammation, and have been shown by several studies to be associated not only with the risk for AD, but also with the progression of the cognitive symptoms of AD (Bermejo, Martin-Aragon, & Benedi, 2008; Holmes et al., 2009; Tan et al., 2008).

The results of the survival analyses indicated no significant association between NSAID use and survival duration in AD. A few previous studies examining mortality and NSAID use among individuals with AD have actually demonstrated an increase in mortality rates, primarily because of cardiovascular risk factors associated with NSAID use (Psaty & Kronmal, 2008). Such results have led to several NSAID medications to be removed from the market and discontinuation of FDA (Federal Drug Administration)

approval (Psaty & Kronmal, 2008). Although the results of this study did not find significant results, there was a trend that individuals taking NSAIDs *prior to AD onset* had a 13% increased hazard of death when compared to those not taking NSAIDs, which would be consistent with findings from previous studies. However, this result did not reach statistical significance ( $p = .07$ ), and it may be that a subgroup of persons, such as those with vascular comorbidity, may exhibit greater risk for mortality than others. An understanding of the relationship between NSAID use and mortality warrants further research in this area.

### **Strengths and Limitations of the Current Study**

There are several strengths and limitations of the study that warrant discussion. Based on the literature, two main issues regarding the pattern of NSAID use were identified: (a) Does the timing of NSAID use matter in relation to AD progression? and (b) Does the duration of NSAID use matter in relation to AD progression? One of the strengths of this study was that it addressed both of these questions. The results from this study also suggest that despite using NSAIDs before or after AD diagnosis there is no impact of NSAID use on the progression of AD.

Addressing the issue of the duration of NSAID use has two benefits. First, as discussed above, it addresses the question posed by Breitner (1996), that perhaps 2 years of continuous use of NSAIDs is necessary to impact the risk of AD. In addition, it also fills a gap in the literature in reference to the RCTs reviewed in this project. Three of the four RCTs on NSAID use and cognitive decline in AD yielded negative results, however, the follow-up times for these RCT's were all 1 year or less, a period of time that has been



argued insufficient to incur beneficial effects. Several researchers have called on studies of longer duration (exceeding 1 year) to examine the question regarding duration of NSAID use and its impact on cognitive decline in AD. Although the current study is not an RCT, and therefore inferences regarding this study cannot be directly compared with results from such studies, this observational study did follow the cognitive trajectory of individuals taking NSAIDs for more than one year, a previous limitation to the studies reviewed earlier.

The results discussed in this project stem from a population-based study conducted in Cache County, Utah. There are obvious benefits from conducting such a study in a population such as avoiding the biases associated with clinic-based samples, allowing one to generalize the results to larger populations. Although this study enjoys this strength, it must also be remembered that the population of older persons studied by the CCSMHA is primarily Caucasian (99%), with the majority consisting of followers of The Church of Jesus Christ of Latter-day Saint religion. Therefore, despite the overall generalizability of population-based studies, the results of this study are not easily generalizable to populations with greater ethnic diversity. Other strengths of the current study include a careful and thorough diagnosis of AD. As reported in the Methods section, diagnoses of AD were only given after a thorough review of data by experienced clinicians in geropsychiatry, neurology, and neuropsychology. In addition, this study included multiple periods of observation post-AD onset that covered prolonged periods of time to allow me to examine duration of NSAID use after the onset of AD.

In addition, one limitation shared by all studies in this area of research is the difficulty in attempting to gather information regarding medication history. Factors such

as recall bias and overall forgetfulness may introduce errors in the report of medication use, especially in a population diagnosed with memory impairment (Fendrich & Rosenbaum, 2003; Romeo, 1997). The methods used in this study (conducting a medicine chest inventory) have been used in a number of other studies of the effects of medication (Fendrich & Rosenbaum, 2003; Romeo, 1997). However, despite this, the inventory of NSAID use, particularly prior to the onset of AD, was examined at 3-year intervals so recall bias may be a more significant issue than the more frequent inventories completed after the onset of dementia.

### **Future Directions**

To further our understanding of the relationship between AD progression and inflammation as well as NSAID use, a future area of research is to examine the relationship between inflammatory markers and their relationship to AD progression. Although much research has been done in the past linking neuroinflammation and risk for AD, little has been done in linking neuroinflammation with the progression of AD symptoms after dementia onset, although there is at least some research that suggests inflammatory biomarkers are associated with decreases in total brain volume in the elderly (Jefferson et al., 2001). Research has shown that some inflammatory markers are predictive of cognitive decline in elderly individuals whereas other studies show no association (Dik et al., 2005; Schram et al., 2007). Research examining whether there are differences between individuals with MCI and AD are mixed. Some research studies have found significant differences between MCI and AD in terms of inflammatory markers, suggesting that greater levels of neuroinflammation is associated with decreases

in cognitive functioning (Guerriero et al., 2007), whereas other studies have failed to find this association (Bermejo et al., 2008).

Research examining the relationship between inflammatory markers and cognitive decline in AD has also been mixed. For example, Holmes and colleagues (2009) examined 300 individuals with mild to moderate AD and their relationship between inflammatory markers and cognitive decline. In their study, they found that acute inflammatory events (e.g., such as blow to the head, short-lived infection [less than 2 months]) were associated with increases in levels of tumor necrosis factor-alpha (TNF-alpha), which were associated with increases in rate of cognitive decline over a 6-month period. Participants who had low levels of TNF-alpha (low levels of inflammatory markers) showed no cognitive decline over the same period (Holmes et al., 2009). However, other studies have not provided such promising results. Lanzrein and colleagues (1998) examined assays from the cerebrospinal fluid from 8 individuals with AD and compared them with samples with 9 controls. Sampling actual cerebrospinal fluid levels of inflammatory markers allowed them to examine inflammation of the brain. They examined a host of different proteins involved in the inflammatory process, including a variety of different cytokines, TNF-alpha, and interleukins (IL-6, IL-1beta). In their study, they found no differences in inflammatory markers between the two samples. Although the latter study suffers from small sample sizes, it does raise certain questions about the source of inflammatory markers (cerebrospinal fluid vs. blood), the extensive number of factors that are involved in the inflammatory process, and whether inflammation plays a more prominent role in early versus later stage disease. Are there some factors that are more important than others? Do some factors, such as TNF-alpha in

the Holmes et al. (2009) study have an impact on AD progression whereas others do not? Future research in the area of inflammatory markers and AD progression should examine these and other questions. In addition, there may be an interactive effect between the presence of APOE  $\epsilon$ 4 alleles, neuroinflammatory markers such as TNF-alpha and other cytokines, and cognitive decline in AD (Blasko et al., 2007).

In summary, the results of this study found no effect of NSAID use on the progression of AD. For future work in this area, it is recommended to first establish a research base examining the link between neuroinflammation and AD progression before examining the effects of compounds that reduce inflammation. If research demonstrates a relationship between these two variables, additional work can be done in the area of NSAID use and progression of AD, in attempting to research not only the relationship between these two variables, but their potential interactive effects with dose of use, age, and study methodology.

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## APPENDICES

## Appendix A:

### MMSE

1- Comp-No PI	5-S Brk-CI*	1-Std Pro
20- Comp-Other*	6-S Brk-PI*	2-Dev Pro*
21-Comp PI≤3/I	61-S Brk-Other*	21-Other Dev Pro
22-Comp PI>3/>I	7-Cog-Untest	22-Sub Dev Pro
2-Comp-PI*	8-Other-NA*	3-NA
3-NP Brk-CI*	9-S Rf	4-3MS for MMSE
4-NP Brk-PI*	10-No Time*	
	11-3MS for MMSE	

COMMENTS: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

TIME:  :  :

### MINI-MENTAL STATE EXAMINATION

Now I would like to ask you some questions to check your memory and concentration. Some of them may be easy and some may be hard.

- What is the year?  
 \_\_\_\_\_  
 ERROR .....0 IMP  
 CORRECT .....1 1-sight  
 INCORRECT: PHYS IMP .....6 2-hearing  
 NOT ASSESSED .....9 3-hands  
 4-other
- What is the season of the year?  
 \_\_\_\_\_  
 ERROR .....0 IMP  
 CORRECT .....1  
 INCORRECT: PHYS IMP .....6 ☐  
 NOT ASSESSED .....9
- What is the date?  
 \_\_\_\_\_  
 ERROR .....0 IMP  
 CORRECT .....1 ☐  
 INCORRECT: PHYS IMP .....6 ☐  
 NOT ASSESSED .....9
- What is the day of the week?  
 \_\_\_\_\_  
 ERROR .....0 IMP  
 CORRECT .....1 ☐  
 INCORRECT: PHYS IMP .....6 ☐  
 NOT ASSESSED .....9
- What is the month?  
 \_\_\_\_\_  
 ERROR .....0 IMP  
 CORRECT .....1 ☐  
 INCORRECT: PHYS IMP .....6 ☐  
 NOT ASSESSED .....9
- Can you tell me where we are right now? (For instance, what state are we in?)  
 \_\_\_\_\_  
 ERROR .....0 IMP  
 CORRECT .....1 ☐  
 INCORRECT: PHYS IMP .....6 ☐  
 NOT ASSESSED .....9
- What county are we in?  
 \_\_\_\_\_  
 ERROR .....0 IMP  
 CORRECT .....1 ☐  
 INCORRECT: PHYS IMP .....6 ☐  
 NOT ASSESSED .....9
- What city/town are we in?  
 \_\_\_\_\_  
 ERROR .....0 IMP  
 CORRECT .....1 ☐  
 INCORRECT: PHYS IMP .....6 ☐  
 NOT ASSESSED .....9
- What floor of the building are we on?  
 \_\_\_\_\_  
 ERROR .....0 IMP  
 CORRECT .....1 ☐  
 INCORRECT: PHYS IMP .....6 ☐  
 NOT ASSESSED .....9



10. What is this address? (If institutionalized, what is the name of the institution?)
- |                           |   |                          |
|---------------------------|---|--------------------------|
| ERROR .....               | 0 | IMP                      |
| CORRECT .....             | 1 | <input type="checkbox"/> |
| INCORRECT: PHYS IMP ..... | 6 |                          |
| NOT ASSESSED .....        | 9 |                          |

11. I am going to name three objects. After I have said them, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.

Please repeat the names for me:  
SCORE FIRST TRY. REPEAT OBJECTS FOR UP TO THREE TRIALS ONLY.

	Trial 1	Trial 2	Trial 3			IMP
APPLE	_____	_____	_____	SCORE .....	<input type="checkbox"/>	
				INCORRECT: PHYS IMP .....	6	<input type="checkbox"/>
TABLE	_____	_____	_____	NOT ASSESSED .....	9	
				# OF TRIALS NEEDED .....	<input type="checkbox"/>	
PENNY	_____	_____	_____	ERRORS DUE TO PHYSICAL IMP .....	<input type="checkbox"/>	

12. Now I am going to give you a word and ask you to spell it forwards and backwards. The word is **WORLD**. First, can you spell it forwards? Now spell it backwards. REPEAT IF NECESSARY. HELP SUBJECT SPELL WORD FORWARD, IF NECESSARY. SCORE NUMBER OF LETTERS GIVEN IN CORRECT ORDER.

W O R L D D L R O W

SCORE .....	<input type="checkbox"/>	IMP
POSITION SCORE .....	<input type="checkbox"/>	
INCORRECT: PHYS IMP .....	6	<input type="checkbox"/>
NOT ASSESSED .....	9	

What were the three objects I asked you to remember?

13. APPLE
- |                           |   |                          |
|---------------------------|---|--------------------------|
| ERROR OR OMISSION .....   | 0 | IMP                      |
| CORRECT .....             | 1 | <input type="checkbox"/> |
| INCORRECT: PHYS IMP ..... | 6 |                          |
| NOT ASSESSED .....        | 9 |                          |
14. TABLE
- |                           |   |                          |
|---------------------------|---|--------------------------|
| ERROR OR OMISSION .....   | 0 | IMP                      |
| CORRECT .....             | 1 | <input type="checkbox"/> |
| INCORRECT: PHYS IMP ..... | 6 |                          |
| NOT ASSESSED .....        | 9 |                          |
15. PENNY
- |                           |   |                          |
|---------------------------|---|--------------------------|
| ERROR OR OMISSION .....   | 0 | IMP                      |
| CORRECT .....             | 1 | <input type="checkbox"/> |
| INCORRECT: PHYS IMP ..... | 6 |                          |
| NOT ASSESSED .....        | 9 |                          |
16. POINT TO A WATCH. What is this called?
- |                           |   |                          |
|---------------------------|---|--------------------------|
| ERROR .....               | 0 | IMP                      |
| CORRECT .....             | 1 | <input type="checkbox"/> |
| INCORRECT: PHYS IMP ..... | 6 |                          |
| NOT ASSESSED .....        | 9 |                          |

17. SHOW A PENCIL. What is this called?
- ERROR.....0  
 CORRECT.....1  
 INCORRECT: PHYS IMP.....6  
 NOT ASSESSED.....9
- IMP ☐
- 
18. I would like you to repeat a phrase after me:  
 (THE PHRASE IS) 'No ifs ands or buts.'  
 ALLOW ONLY ONE TRIAL. PHRASE MAY BE  
 REPEATED IF REQUESTED BY SUBJECT  
 BEFORE A FIRST ATTEMPT.
- ERROR OR OMISSION.....0  
 CORRECT.....1  
 INCORRECT: PHYS IMP.....6  
 NOT ASSESSED.....9
- IMP ☐
- 
19. Read the words on this page, than do what it  
 says. THE PAPER READS: "CLOSE YOUR  
 EYES." SCORE CORRECT IF SUBJECT  
 CLOSES EYES.
- ERROR OR OMISSION.....0  
 CORRECT.....1  
 INCORRECT: PHYS IMP.....6  
 NOT ASSESSED.....9
- IMP ☐
- 
20. I am going to give you a piece of paper. When I  
 do, take the paper in your right hand, fold the  
 paper in half with both hands, and put the paper  
 down on your lap.  
 READ FULL STATEMENT, THEN HAND  
 PAPER TO SUBJECT. DO NOT REPEAT  
 INSTRUCTIONS OR COACH.
- Right hand
- ERROR.....0  
 CORRECT.....1  
 INCORRECT: PHYS IMP.....6  
 NOT ASSESSED.....9
- IMP ☐
- Folds
- ERROR.....0  
 CORRECT.....1  
 INCORRECT: PHYS IMP.....6  
 NOT ASSESSED.....9
- IMP ☐
- In lap
- ERROR.....0  
 CORRECT.....1  
 INCORRECT: PHYS IMP.....6  
 NOT ASSESSED.....9
- IMP ☐
21. Write any complete sentence on that piece of  
 paper for me.
- ERROR.....0  
 CORRECT.....1  
 INCORRECT: PHYS IMP.....6  
 NOT ASSESSED.....9
- IMP ☐
22. Here is a drawing. Please copy the drawing on  
 the same paper. SCORE CORRECT IF THE  
 DRAWING INCLUDES TWO FIVE-SIDED  
 FIGURES AND IF ALL ANGLES IN THE FIVE-  
 SIDED FIGURE ARE PRESERVED.
- ERROR.....0  
 CORRECT.....1  
 INCORRECT: PHYS IMP.....6  
 NOT ASSESSED.....9
- IMP ☐

Total Score  /

Pos Score  /

## Appendix B:

CDR-SB

<b>SECTION COMPLETED</b>	YES (ENTIRE SECTION) .....
	INCOMPLETE OR BREAK-OFF .....
	NO (NO DATA/RF) .....

### SECTION AD: Consensus CDR Staging

	Memory	Orientation	Judgment and Problem Solving	Community Affairs	Home and Hobbies	Personal Care
None (0)	No memory loss or slight, inconstant forgetfulness	Fully oriented	Solves everyday problems well; judgment good in relation to past performance	Independent function at usual level in job, shopping, business and financial affairs, volunteer and social groups	Life at home, hobbies intellectual interests well maintained	Fully capable of self care
Questionable (0.5)	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Fully oriented except for slight difficulty with time relationships	Slight impairment in solving problems, similarities, differences	Slight impairment in these activities	Life at home, hobbies, intellectual interests slightly impaired	Fully capable of self care
Mild (1)	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Moderate difficulty in handling problems, similarities, differences; social judgment usually maintained	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Needs prompting
Moderate (2)	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe difficulty with time relationships; usually disoriented in time, often to place	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	No pretense of independent function outside home. Appears well enough to be taken to functions outside family home	Only simple chores preserved, very restricted interests, poorly sustained	Requires assistance in dressing, hygiene, keeping of personal effects
Severe (3)	Severe memory loss; only fragments remain	Oriented to person only	Unable to make judgments or solve problems	No pretense of independent function outside home. Appears too ill to be taken to functions outside family home	No significant function in home	Requires much help with personal care; frequent incontinence
Sub-item	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
	1	2	3	4	5	6

Scores

**Although rules for assigning CDR stages beyond CDR 3 have not been established, the following have been proposed to distinguish additional levels of Impairment in advanced dementia :**

Profound (4)	Speech usually unintelligible or irrelevant; unable to follow simple instructions or comprehend commands; Occasionally recognizes spouse or caregiver. Uses fingers more than utensils, requires much assistance. Frequently incontinent despite assistance or training. Able to walk a few steps with help; usually chair-bound; rarely out of home or residence; purposeless movements often present.		
Terminal (5)	No response or comprehension. No recognition. Needs to be fed, may have NG tube and/or swallowing difficulties. Total incontinence. Bedridden, unable to sit or stand, contractures.		
Sensory-Mtr confound (91)	Functional impairment could not be determined due to sensory/ motor impairment		
<b>Current Staging of Dementia:</b> (Computer will score if desired)	0    => No Dementia	3    => Severe Dementia	<input type="text"/>
	0.5   => Uncertain or deferred diagnosis	4    => Profound dementia	
	1    => Mild Dementia	5    => Terminal Dementia	
	2    => Moderate dementia	91   => Sensory- Mtr Confound	

## CURRICULUM VITAE

**Trevor Buckley****Curriculum Vitae**

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 t.buckley@aggiemail.usu.edu

**EDUCATION*****Utah State University, Logan, UT***

Ph.D. Candidate, Combined Clinical, Counseling, and School Psychology

- Doctoral Dissertation: Does NSAID Use Affect Dementia Progression and Survival Rates? The Cache County Study.
- Chairperson: JoAnn Tschanz, Ph.D.
- Dean's list all semesters

**Utah State University, Logan, UT**

M.S. in Combined Clinical, Counseling, and School Psychology, 2008

- Masters thesis: Measuring unawareness of cognitive decline in a population of elderly individuals: The Cache County Study.
- Chairperson: JoAnn Tschanz, Ph.D.
- Dean's list all semesters

***University of Utah, Salt Lake City, UT***

B.S. Major: Psychology, Minor: Spanish

- Dean's list
- Graduated *cum laude*
- Member Psi Chi, 2002-2004

**HONORS & PROFESSIONAL SOCIETIES**

Simmons Family Scholarship from 2006-2010 (\$8000)

Health Practitioner Military Scholarship (HPSP Scholarship) 2007-2009

Vice-Presidential Fellowship 2005-06 (\$15,000)

Travel Award. International Conference on Alzheimer's disease (ICAD), July, 2008, (\$600)

Travel Award. International Neuropsychological Society (INS), October, 2007  
(\$600)  
Golden Key National Honor Society

### CLINICAL EXPERIENCE

**2008 – 2009**, Student Intern: Bear River Mental Health, Logan, UT

Supervisor: Scott Blickenstaff, Ph.D.

Clinical Population: Adults with severe mental illness. Neuropsychological assessments on children and adolescents.

Clinical Hours: 325, Total Support Hours: 815

- Conducted psychological intakes, psychotherapy, psychological and neuropsychological assessments.
- Served as the sole provider of psychological services for the Cache County Jail, a 360-bed facility used to house inmates within Cache County, Utah. Conducted psychological assessments on inmates.
- Helped design and implement a Mental Health Court program at the Cache County Jail. Implemented it in the Spring of 2009. Also designed and helped write the methods for a Quality Assurance project on the Mental Health Court program in Cache Valley. Began gathering data in the Summer of 2009.

**2008 – 2009**, Behavioral Health Consultant: Cardiac Rehabilitation Center at Brigham City Community Hospital, Brigham City, UT

Supervisor: M. Scott Deberard, Ph.D.

Clinical Population: Elderly individuals who recently had cardiac surgery or some other cardiac procedure.

Clinical Hours: 51, Total Support Hours: 115

- Provided psychological assessments and brief psychotherapy for individuals undergoing cardiac rehabilitation.
- Conducted a stress-management group with clients undergoing cardiac rehabilitation.

**2008 – 2009**, Behavioral Health Consultant: Student Health and Wellness Center at Utah State University, Logan, UT

Supervisor: M. Scott Deberard, Ph.D.

Clinical Population: Student body attending Utah State University.

Clinical Hours: 24, Total Support Hours: 60

- Provided short-term individual psychotherapy (4-8 sessions) and psychological screening in a primary care setting. Conducted intake interviews and provided referral services to clients requiring more extensive therapy.

- Educated clients about topics related to health psychology: chronic pain; stress management; substance abuse; and sexually transmitted diseases.
- Served as consultant to physicians, nurses, and other medical staff regarding treatment of clients with emotional concerns.

**2006 – 2008**, Student Intern: Center for Persons with Disabilities at Utah State University, Logan, UT  
 Supervisor: Robert C. Cook, Ph.D.  
 Clinical Population: Children, adolescents and adults with disabilities.  
 Clinical Hours: 257, Total Support Hours: 640

- Conducted psycho-educational and neuropsychological evaluations with children, adolescents, and adults. Present assessment findings in written reports. Provide evaluation feedback to clients, parents, and school personnel.
- Presented clinical cases and provided case conceptualizations for discussion in multi-disciplinary team meetings.
- Consulted with parents and school personnel to create treatment plans to assist children and adolescents enhance learning and academic performance.
- Provided assessments for the specific evaluation of possible Autism or Autism Spectrum disorders.

**2007 – 2008**, Student Therapist: Counseling Center at Utah State University, Logan, UT  
 Supervisor: David Bush, Ph.D.  
 Clinical Population: Student body attending Utah State University.  
 Clinical Hours: 104, Total Support Hours: 220

- Conducted intake interviews and provided brief and long-term counseling to college students presenting with various DSM Axis I and Axis II disorders.
- Presented clinical cases and led discussions in seminars with a team of licensed psychologists, psychology interns, and fellow practicum students.
- Practiced in a group practicum setting various modes of therapy: Dialectical Behavioral Therapy; Schema Therapy; Mindfulness; treatment of PTSD, eating disorders, and addictions.
- Delivered outreach presentations on stress management and Counseling Center resources to university students. Conducted screenings for depression, anxiety, and alcoholism.

**Spring 2006**, Student Therapist: Utah State University Psychology Community Clinic. Logan, UT  
 Supervisor: Melanie Domenech-Rodríguez Ph.D.  
 Clinical Hours: 43 Total Support Hours: 110

- Conducted psychological intakes of students and members of the community suffering from a variety of psychological disorders.



- Conducted long and short-term psychotherapy to adults experiencing various psychological concerns.

**2005 – 2007**, Neuropsychological Technician: Center of Epidemiological Studies, Logan UT

Supervisor: JoAnn Tschanz, Ph.D.

Clinical Hours: 275, Total Support Hours: 610

- Conducted neuropsychological testing on elderly individuals.
- Conducted semi-structured interviews with informants of research participants with normal and impaired cognition.
- Participated in review of case material for diagnosing dementia and other cognition disorders.

### RESEARCH EXPERIENCE

**2005-present**, Research Assistant: Dementia Progression Study and Cache County Study on Memory in Aging, Logan, UT.

Principal investigator: JoAnn Tschanz, Ph.D.

- Write and submit research abstracts for scientific conferences.
- Conduct literature reviews.
- Organize and examine data using SPSS data analysis.
- Participate in a multi-disciplinary team comprised of physicians, nurses, psychologists and graduate students researching the causes and corollaries of dementia.

**2004-2005**, Research Assistant: Social Psychology Lab, University of Utah, Salt Lake City, UT

Principle investigator: Jonathan Butner, Ph.D.

- Conducted literature reviews. Created a new dynamic measure for individualism and collectivism assessment.
- Created and managed online mass testing survey questionnaire.
- Used factorial analysis to statistically structure new measure for individualism and collectivism

**2003-2004**, Research Assistant: Neuropsychology Lab at the University of Utah, Salt Lake City, UT

Principal investigator: Yana Suchy, Ph.D.

- Assisted in the creating of a computer device used to assess neuropsychological deficit in patients who had sustained a traumatic brain injury.
- Conducted literature reviews, created computer software used to score neuropsychological tests, ran research participants on a new measure used to assess frontal-lobe dysfunction, and examined data.

**2003-2004**, Research Assistant: Neurobehavioral Lab at the University of Utah, Salt Lake City, UT

Principal investigator: Raymond Kesner, Ph.D.

- Conducted hippocampal surgeries on animal subjects (rats). Injected animal subjects with dopamine agonists and ran subjects on series of complex mazes.
- 
- Conducted data analysis and interpretation.

#### OTHER PROFESSIONAL EXPERIENCE

**2004-2005**, Psychiatric Technician: 5 West Psychiatric Unit, University of Utah Hospital, Salt Lake City, UT

- Conducted groups focusing on assisting inpatient psychiatric patients with interpersonal skills, daily living skills, and stress-management skills.
- Monitored and charted patient activities, and met with patients ensure patient emotional, mental, and physical needs were met.
- Met daily in a multi-disciplinary team meeting with physicians, social workers, and nurses to discuss patient's functional, cognitive, and emotional concerns.

**2001-2004**, Medicaid Representative: Department of Neurology, University of Utah Hospital, 3<sup>rd</sup> Floor, Salt Lake City, UT

- Assisted low-income patients of neurological and psychiatric units of the University of Utah Hospital with financial coverage of hospital services.
- Provided counseling service and crisis intervention for families following TBI.
- Assisted patients who had undergone a TBI follow through with Medicaid and SSI disability forms.

**2003-2004**, Educational Assistant: The NeuroDevelopment Center, Salt Lake City, UT

- Educated local elementary and junior high school administrative staff in the presentation and basic intervention skills of seizure activity in children and adolescents.
- Created educational packet, compiled literature and educational material for administrative personnel of elementary schools in the surrounding Salt Lake area.

### TEACHING EXPERIENCE

- Fall, 2009** Teaching Assistantship. Taught one course of Psychology 1730: Strategies of Academic Success. Undergraduate-level course. Focused on teaching the reading, test-taking, note-taking, and anxiety management skills necessary for college success.
- Fall, 2008** Teaching Assistant. Psychology 6310, Intellectual Assessment. Graduate-level course. Assisted graduate students learn to administer and score standardized intellectual tests. Conducted labs to educate students on the construct of intelligence, and the viability and utility of its measurement within the field of psychology.
- Spring, 2008** Guest Lecturer: Psychology 1010, Introduction to Psychology. Lectured on DSM diagnoses, Categorical versus Dimensional approach to psychiatric diagnoses, and issues regarding the contributory versus causality factors of psychiatric disorders.
- Fall, 2006** Guest Lecturer: Psychology 6310, Intellectual Assessment. Lectured on the development of the Wechsler Adult and Child intelligence scales, and on the dominant theories regarding the construct of intelligence.
- Spring, 2006** Guest Lecturer: Psychology 1010, Introduction to Psychology. Lectured on the incidence and prevalence of brain injuries among different socioeconomic and age groups. Lectured on the impact of traumatic brain injury (TBI) and cognitive, social, and emotional outcomes.
- Fall, 2004** Teaching Assistant. Psychology 3904, Surveys of Clinical Psychology and Service Learning. Graded assignments and tests regarding the application and practice within the psychological profession. Lectured on science and its impact on society, differences between Basic and Applied Science, and on the fusion between societal values and scientific curiosity.

### OUTREACH/COMMUNITY LECTURE EXPERIENCE

- Fall, 2008** Clinical Presentation. Presented on the WAIS-IV revision and differences between the WAIS-IV from the WAIS-III to licensed psychologists and employees at Bear River Mental Health.
- Spring, 2008** Conducted intakes and alcohol screening for students. Provided appropriate referral sources as necessary.
- Spring, 2008** Participated in a free depression-screening for students. Provided appropriate referral sources as necessary.
- Fall, 2007** Guest Presenter: Physical Education, 2020. Co-presented on the services provided at the Utah State Counseling Center. Presented on self-injurious behaviors as a coping method for university students.
- Fall, 2007** Participated in a free anxiety-screening for students. Provided appropriate referral sources when necessary.

### CONFERENCE PRESENTATIONS & ABSTRACTS

Tschanz, J. T., Corcoran, C., Green, H., Munger, R., Mielke, M., Norton, M., Rabins, P., Welsh-Bohmer, K., **Buckley, T.**, Breitner, J., Lyketsos, M. (January, 2009). *Interaction between C-Reactive Protein level and APOE genotype in predicting rate of progression in Alzheimer's disease. The Cache County Dementia Progression Study.* Presentation at the International Conference on Alzheimer's Disease (ICAD) in Vienna, Austria.

Morrison, A., **Buckley, T.**, Piercy, K., Norton, M., Rabins, P., Tschanz, J., Lyketsos, C. (February, 2009). *Predictors of Quality of Life Ratings for Persons with Dementia Simultaneously Reported by Patients and their Caregivers: The Cache County (Utah) Study.* Presentation at the Conference of the Southern Nursing Research Society (SNRS), Baltimore, Maryland.

**Buckley, T.**, Norton, M., Deberard, M.S., Welsh-Bohmer, K., Lyketsos, C., Tschanz, J. (July, 2008). *Assessment of awareness of cognitive change in individuals with and without dementia: The Cache County Study.* Poster session presented at the International Conference on Alzheimer's disease (ICAD), Chicago, Illinois.

Tschanz, J., Cook, L., Corcoran, C., Norton, M., Mielke, M., Rabins, P., Welsh-Bohmer, K.A., Treiber, K., **Buckley, T.**, Breitner, J.C.S., Lyketsos, C. *Gender Differences in the Trajectory of Cognitive Decline in Alzheimer's Disease in the Cache County Population.* Presentation at the 36th Annual Meeting of the International Neuropsychological Society, Waikola, Hawaii, Feb., 2008.

**Buckley, T.**, Tschanz, J., Norton, M., Corcoran, C., Welsh-Bohmer, K., Breitner, J., (September, 2007). *Metacognitive Judgments and Change in Cognitive and Functional Abilities in a Population of Elderly Individuals. The Cache County Study*. Poster session presented at the International Neuropsychological Society (INS) Conference, Portland, Oregon.

Tschanz, J., Cook, L., Corcoran, C., Norton, M., Mielke, M., Rabins, P., Welsh-Bohmer, K., Treiber, K., **Buckley, T.**, Breitner, J.S.C., Lyketsos, C. (September, 2007). *Gender Differences in the Trajectory of Cognitive Decline in Alzheimer's Disease in the Cache County Population*. Poster session presented at the International Neuropsychology Conference (INS) Portland, Oregon.

Tschanz J., Cook L., Corcoran C., Norton M., Mielke M., Rosenberg, P., **Buckley T.**, Clay, C., Welsh-Bohmer, K., Breitner, J., Lyketsos, C. (August, 2006). *Vascular Factors and the Rate of Decline in Dementia; The Cache County Study*. Presentation at the International Conference on Alzheimer's Disease (ICAD) in Madrid, Spain.

#### PEER-REVIEWED PUBLICATIONS:

**Buckley, T.**, Norton, M., Deberard, M., Welsh-Bohmer, Lyketsos, C., Tschanz, J.T. (2009). A Brief Metacognition Questionnaire for the Elderly: Comparison with Cognitive Performance and Informant Ratings: The Cache County Study. *International Journal of Geriatric Psychiatry*, in press.

#### PRINTED DISPATCH

**Buckley, T.**, Tschanz, J.T. (2008). Anosognosia: Assessment Tools for Its Epidemiologic Study in Geriatric Populations with Dementia, *Primary Psychiatry*, 9, 24-29.

#### PROFESSIONAL AFFILIATIONS

American Psychological Association, Student Affiliate

#### PROFESSIONAL DEVELOPMENT

04/2009      **Attendee**, Psychology Department at Utah State University training seminar, Logan , UT.  
Acceptance and Commitment Therapy (ACT). Full day seminar on ACT. Presented by Dr. Steven Hayes, co-founder of ACT.

- 10/2008      **Attendee**, Bear River Mental Health Training Seminar, Logan, UT.  
Brain Games: New Avenues in Brain Rehabilitation: Full day seminar that introduced therapeutic training techniques for individuals in the neurological rehabilitation process following a TBI. Presented by Nancy-Louise Howse, Ph.D.
- 09/2008      **Attendee**, Utah Psychological Association Training Seminar, Salt Lake City, UT.  
WAIS-IV Update: 3-hour seminar on the new version of the Wechsler Adult Intelligence Scales. Presented by Patrick J. Moran, Ph.D., The Psychological Corporation.
- 04/2008      **Attendee**, 14<sup>th</sup> Annual Utah State University Counseling Center Conference, Logan, UT.  
Mindfulness-Based Cognitive Therapy: 1-day workshop on the use of mindfulness in cognitive behavioral psychotherapy. Presented by Mark Lau, Ph.D., University of British Columbia.
- 02/2007      **Attendee**, Utah State University Center for Epidemiological Studies Seminar, Logan, UT.  
Epidemiology of Alzheimer's Disease: 2-hour seminar on the etiology of Alzheimer's disease and current pharmaceutical treatments. Presented by Constantine Lyketsos, M.D., MPH, Johns Hopkins University.
- 09/2006      **Attendee**, Utah State University Center for Persons with Disabilities Seminar, Logan, UT.  
Traumatic Brain Injury and Rehabilitation: 1-day multidisciplinary seminar on traumatic brain injury and techniques/resources for working with survivors and their families, presented by the Interdisciplinary Training unit at the Center for Persons with Disabilities. Presented by: David Nilsson, Ph.D.
- 05/2006      **Participant**, Workshop in Dementia Research, Provo, UT.  
Rating System for MRI Images: 4-hour workshop on a system for rating brain scans of participants in the Cache County Study on Memory, Health, and Aging. Presented by Erin Bigler, Ph.D., Brigham Young University.

REFERENCES

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